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Section of Anæsthetics

President—Professor R. R. MACINTOSH, M.A., D.M., F.R.C.S.Ed., F.F.A.R.C.S., D.A.

[*April* 2, 1954]

The Pharmacology of Chlorpromazine and Promethazine

By J. H. BURN, M.D., F.R.S.

Department of Pharmacology, University of Oxford

THE story of chlorpromazine and promethazine begins, so far as I am concerned, about eight years ago, with the results of an investigation carried out by Dawes (1946) in the Oxford laboratory, to find substitutes for quinidine for use in auricular fibrillation. Many substances were found to share with quinidine the power to prolong the refractory period of cardiac muscle. Among them were local anæsthetics such as procaine and amethocaine, spasmolytics such as atropine and papaverine, and analgesics such as pethidine. In fact, it appeared at first that in the possession of a quinidine-like action there was a common meeting ground for a large number of substances which were otherwise dissimilar. Dawes showed, however, that more than one property was shared by these different substances, and that, for example, all of them had a local anæsthetic action also.

A few months later we were excited by the arrival of some of the new antihistamine substance Neo-antergan (mepyramine), and it occurred to me to wonder whether it would share these properties too. My colleagues Dews and Graham (1946) found that it did. As a substance prolonging the refractory period of cardiac muscle, it was twice as active as quinidine, and as a local anæsthetic it was 3·1 times as active as procaine. Thus the class of substances widened, and was extended still further by Hutcheon (1953) to include a group of four related substances, one of which was promethazine and another was Diparcol (diethazine) which is used in the treatment of Parkinson's disease.

Fall of body temperature.—The disclosure of so many common properties in substances used for so wide a range of therapeutic effects was of great interest from the pharmacological point of view, since it offered the prospect of introducing some order into the chaos of the actions of alkaloids. The textbooks of pharmacology during the last half-century give few clues to the relation of one substance to another; procaine is described as a local anæsthetic and atropine as a spasmolytic or as a substance which inhibits the action of cholinergic nerves. The relation of procaine to atropine is, however, rarely or never discussed. It therefore seemed desirable to see how much farther the parallelism in the properties of these substances would prevail. As a next step an investigation was made into their effect on body temperature. For in 1931 Glaubach and Pick showed that when procaine was injected into guinea-pigs, it had the peculiar action of causing body temperature to fall. This property seemed sufficiently remote from other properties of procaine that there was a good chance that it would not be shared by other substances.

Our results (Burn and Dutta, 1948*a*; Dutta, 1948) soon showed that the action of procaine was shared by pethidine, atropine, Benadryl (diphenhydramine) and quinidine. Observations were made in mice recording the rectal temperature by a thermocouple. Equal numbers of injected and control mice were kept side by side, and the difference in the mean temperature of the injected mice from the mean temperature of the control mice was calculated. Observations were also made in mice after adrenalectomy, and the difference in the temperature was then found to be greater than before, and of longer duration. The results with Benadryl (20 mg./kg.) were similar in all respects to those with pethidine, but when atropine and quinidine were used in similar dose to pethidine they caused very little fall of temperature unless the mice were adrenalectomized. The fall then was prolonged and with quinidine profound.

Thus the property of lowering body temperature which procaine possessed was also shared by quinidine, by an antihistamine, by atropine and by an analgesic substance. The similarity between these different agents was strengthened.

Abolition of constrictor action of adrenaline.—To test the similarity farther we chose another unusual property of one substance, to see if it was shared by the others. Bussell (1940) had shown that atropine exerted a vasodilator action in vessels in which a tone was maintained by adrenaline, and he had also shown that in the vessels of the perfused rabbit ear, atropine could abolish the vasoconstrictor action of adrenaline. We examined pethidine, procaine, Benadryl and quinidine to see if they acted like atropine (Burn and Dutta, 1948*b*). Each of these substances was found to abolish the vasoconstrictor action of adrenaline; atropine, Benadryl and pethidine were similar to one another in potency, quinidine being weaker and procaine very much weaker. Here again, was evidence of a resemblance of the properties of these different agents.

Ganglion-blocking action.—Experiments were also made (Dutta, 1949*a*) to see if these substances possessed a ganglion-blocking action. For this purpose the superior cervical ganglion of the cat was perfused by Kibjakow's well-known method, and stimuli were applied to the cervical sympathetic chain. A record of the contractions of the nictitating membrane was obtained to indicate the effectiveness of the transmission of impulses through the ganglia. Again, it was found that atropine, pethidine, procaine and quinidine were able to diminish the effect of preganglionic stimuli, though atropine which was active in an amount of 50 μg. was five to ten times more powerful than the others. In a later paper Dutta (1949*b*) described a similar action of the two antihistamine substances diphenhydramine (Benadryl) and antazoline (Antistin); their potency was about one-fifth that of atropine.

Similarity of properties.—The similarity of the properties of many local anæsthetics, quinidine-like substances, analgesics, spasmolytics and antihistamine substances was therefore borne out by all investigations. The results made it possible to predict with some approach to accuracy the general properties of other substances which possessed one of these actions. Thus we could say that any new antihistamine would have a quinidine-like action, would be a local anæsthetic, would lower body temperature and so on. Hutcheon (1953) examined four substances related to promethazine, and was able to compare their actions as local anæsthetics, as inhibitors of salivary secretion, as spasmolytics, and as quinidine-like substances.

When, therefore, chlorpromazine was introduced into clinical use by Laborit and Huguenard (1951) it was possible to forecast its general properties from the fact that it was a close chemical relation of promethazine, with the result that when the paper on its pharmacological action by Courvoisier *et al.* (1953) appeared, it contained few surprises.

These workers showed as might be expected that it abolished or reversed the action of adrenaline on the blood pressure and reduced its vasoconstrictor action. It possessed a quinidine-like action, but very little antihistamine action; it had a striking action in lowering body temperature, it was a local anæsthetic, and it had a central sedative effect. It had other effects like those of promethazine, being anti-emetic and increasing capillary resistance to the action of ovalbumin and other agents.

Because of the use which has been made of chlorpromazine in operations, and of the interest which it has aroused, we felt it worth while to examine it at Oxford, and to note for ourselves what effects it produced.

Effect on temperature.—We turned our attention first to its action on body temperature, and since it has been usually given together with pethidine and promethazine in anæsthetic procedures, my colleagues, Mr. A. K. Armitage and Dr. J. Kopera, compared the three substances. The results of Courvoisier and her colleagues indicated that in mice chlorpromazine was 25 times as effective as promethazine, which seemed to us a surprisingly high figure. Our results were obtained by recording the rectal temperature of mice with thermocouples and using in each experiment the same number of injected mice and of control mice. We determined the effect of a given amount of each substance by the difference in the mean temperature of the two groups. We found that chlorpromazine given in the dose of 1 mg./kg. exerted a greater and much more prolonged effect than 30 mg./kg. of either promethazine or pethidine. These two substances were similar in activity.

There has been much discussion and some confusion about the cause of this fall of temperature. One view is that suggested by Courvoisier *et al.* (1953) who said that "one can then liken the effects of chlorpromazine to an actual chemical adrenalectomy". This idea appeals to those who believe that activity of the adrenal cortex indicates the existence of stress, that stress is invariably bad for the organism, and that activity of the adrenal cortex should always be avoided. Thus Wells (1954) referring to the use of chlorpromazine "which puts the heat-regulating mechanism out of action" says "if it can be shown that in hibernation the stress response is minimal . . .".

Now we know that the adrenal gland is active at low temperature. Adrenal cortical extracts are tested biologically by their ability to prolong the life of young adrenalectomized rats exposed to a temperature of 2° C. But the adrenal glands are also active when body temperature is reduced by drugs. This was shown by Dutta and myself for atropine, quinidine, Benadryl, procaine and pethidine. The fall of temperature caused by these substances was greater—and often much greater—in adrenalectomized mice (compared with adrenalectomized controls) than in normal mice. This proved that the fall of temperature occurred in spite of the activity of the adrenal glands and not because that activity had been paralysed. It may well be that there is a maximal activity of the adrenals during drug hypothermia and that in this sense the body is subjected to maximal stress.

The other view of the cause of the fall of temperature is that it is due to a block of the neuro-vegetative system, which we call the autonomic system. This view has been expressed by Laborit and Huguenard (1951) and accepted by various workers in this country. Whatever is meant by such a block, it is clearly not ganglionic blockade, since a full dose of hexamethonium (5 mg./kg.) has little effect in lowering temperature in mice.

It is, of course, perfectly possible that interference or block of the sympathetic system may play a part in the fall of temperature, for the experiments of Sawyer and Schlossberg (1933) showed that cats which were sympathectomized had much greater difficulty in controlling their temperature

than normal cats. At 8°–9°C., sympathectomized cats shivered the whole time and nevertheless the rectal temperatures fell. Normal cats, on the other hand, shivered only occasionally and their temperatures rose.

There is, however, no evidence that chlorpromazine blocks the sympathetic system. It is true that it is an anti-adrenaline substance and that it can reduce or abolish the vasoconstrictor action of adrenaline. However, even its anti-adrenaline action is limited for Courvoisier *et al.* (1953) showed that chlorpromazine did not reduce the action of adrenaline in releasing glucose from the liver. Anti-adrenaline substances in any case have very little action on the sympathetic system, for this acts by liberating noradrenaline, which is not appreciably affected by chlorpromazine.

Effect on skeletal muscle.—Since the maintenance of body temperature is primarily the concern of skeletal muscles, we were anxious to see what effect chlorpromazine would have on them. In their paper Courvoisier and her colleagues recorded that chlorpromazine did not alter the toxicity of the curarizing agent gallamine given intravenously, but that in a dose of 10 mg./kg. it diminished the amount required to cause "head-drop" (that is, a paralysis of the neck muscles) to about 40% of the normal. Furthermore, in a dose of 20 mg./kg. it prolonged the duration of curarization from 3·25 to 4·5 hr.

We made observations on cats, first anæsthetized with chloralose and then decerebrated, in which we recorded the contractions of the gastrocnemius muscle by attaching the tendo Achillis to a tension lever; we stimulated the muscle both through the sciatic nerve and directly. We soon confirmed the observation that the injection of chlorpromazine in the amount of 1·3 mg./kg. prolonged the action of d-tubocurarine, but we also found that doses of 3 mg./kg. caused a gradual failure not only of contractions evoked by nerve stimulation, but also of those caused by direct stimulation, so that the muscle became inexcitable no matter how great a stimulus was applied. The results showed that chlorpromazine exerted a direct paralytic action on skeletal muscle, though the onset of this effect was delayed and sometimes preceded by an initial phase of augmentation. Dutta (1949*a*) described a similar effect due to pethidine when using the isolated rat diaphragm.

Similar effects to those of chlorpromazine were obtained with promethazine and with pethidine, though only when larger amounts were used. Chlorpromazine appeared to be two to three times as active as promethazine, and six times as active as pethidine, but it is not possible by experiments of this kind in cats to make a quantitative comparison of different substances. In a preliminary experiment on Dr. E. Bülbring's preparation of the rat diaphragm stimulated through the phrenic nerve, chlorpromazine was found to be 3·5 times more active than promethazine.

These results on skeletal muscle were striking in view of the amounts required. Dundee *et al.* (1953) used for their patients 50 mg. chlorpromazine, 100 mg. pethidine and 50 mg. promethazine, given intravenously. This was three to four hours after premedication with pethidine 100 mg. and promethazine (amount unspecified) by intramuscular injection. The results in the cat suggest that these amounts given to patients produce a paralysis of the skeletal muscles which might account for the fall of body temperature observed. Caution should, however, be exercised in assuming that all the skeletal muscles are paralysed to the same extent as the gastrocnemius. We did not observe that respiration was arrested by these substances and therefore the diaphragm was not paralysed.

However, we may conclude that an effect on skeletal muscles plays a part, and perhaps a large part, in causing the fall of temperature. In view of the general depressant action of chlorpromazine on the central nervous system it seems probable that there is also an effect on the heat-regulating centre, though there is no evidence that this effect is a "central autonomic block".

The toxic action of chlorpromazine.—In their long paper of 57 pages, Courvoisier and her colleagues devoted only half a page to the important subject of chronic toxicity. They administered chlorpromazine to dogs and said that a daily injection of 20 mg./kg. for a month did not cause any death. They did not say how many dogs were used. Histological examination revealed changes both in the kidneys and in the lungs. Changes were produced in the kidneys by amounts as low as 2 mg./kg. What was, however, very surprising was that there was no reference to the liver, for it is in the liver that toxic effects might be expected.

However, Moyer *et al.* (1954) describe observations made in 15 control subjects and 9 patients, which showed that when chlorpromazine was given orally in 25 mg. four times daily for a week there was no evidence of liver damage. There was no rise of serum bilirubin or change in thymol turbidity or bromsulphalein tests. Nor was there evidence of any change in renal function.

One of the simplest ways of determining chronic toxicity is by carrying out growth tests in young rats, and we have made comparative tests with the three substances. We found that as much as 100 mg./kg. pethidine daily had no effect on growth, while promethazine in a daily total of 90 mg./kg. in 2 doses caused retardation of growth. Chlorpromazine was rather more toxic and caused retardation of growth and an occasional death in a daily total of 20 mg./kg. in 2 doses. With both chlorpromazine and promethazine the retardation of growth or loss of weight was seen during the first three or four days, after which the rats grew at about the same rate as the controls although the injections of the two substances were continued. The results, however, indicated that chlorpromazine had more toxicity than was to be supposed from the work of Courvoisier and her colleagues. Our own results are not yet complete.

Other effects.—We tested chlorpromazine in other ways. We compared it with promethazine and pethidine for prolonging the time of sleep produced by pentobarbitone and found that it was three times more powerful than these two substances. However, we failed to find any potentiation of the action of morphine by chlorpromazine.

Again, we compared it with pethidine and promethazine for its local anæsthetic action, using intracutaneous injection in the guinea-pig, which measures the action on sensory nerve endings. Chlorpromazine was found 1·16 times stronger than promethazine, and 2·12 times stronger than pethidine.

The anti-adrenaline action of these substances was compared in three ways, and again chlorpromazine was more powerful than promethazine, and very much more powerful than pethidine. The comparison was made first by their reduction of the pressor effect of adrenaline in the spinal cat; second, by their reduction of the constrictor effect of adrenaline in the perfused vessels of the rabbit ear, and third, by their reduction of the simulant action of adrenaline on the isolated rabbit uterus.

The antihistamine action of these substances was tested on the guinea-pig bronchioles using the method of Konzett and Roessler (1940). We found that promethazine was 100 times more active than chlorpromazine. This fully confirms the finding of Courvoisier and her colleagues.

Discussion

The position of chlorpromazine can be looked at first from the point of view of its pharmacological properties. The pharmacological evidence concerning chlorpromazine which has been published hitherto was not surprising, and did not indicate that there was any therapeutic use for which it was particularly suited. The first property described by Courvoisier *et al.* which it possessed to an unusual extent was its anti-adrenaline action, which might make it useful in the treatment of Raynaud's disease. A factor contrary to such a use would be the accompanying drowsiness and mental depression which would disturb some patients. The other unusual property was its power to lower body temperature. This would not have seemed a property of any clinical value to most pharmacologists since a lowering of body temperature by a drug would be regarded as a harmful action.

It is true that recently the lowering of body temperature by physical means has been adopted as a procedure to facilitate operations on the heart or main blood vessels (Bigelow *et al.*, 1950). When a large part of the circulation must be interrupted, it is a sound physiological principle to reduce the tissue demand for oxygen by reducing the temperature. Having this in mind, Laborit seems to have reached the conclusion that it is equally justifiable to reduce body temperature by using a drug or rather a mixture of drugs. The reduction of body temperature by the action of a drug surely indicates that the tissues are being poisoned, for the body makes every effort to maintain a constant temperature in ordinary circumstances.

The use of these drugs, moreover, has one aspect to which little reference has been made, namely, that once they are given, the patient's condition is out of the anæsthetist's control. At one time substances like pentobarbitone and bromethol were used for producing full anæsthesia; they were indeed introduced for this purpose. It was then found that a proportion of patients were unusually sensitive and that the ordinary anæsthetic dose was fatal to them. These substances then reverted to the position of basal anæsthetics, and were given in lower dose to ensure that there were no more deaths. More rapidly destroyed barbiturates like hexobarbitone and thiopentone were introduced and are now regularly used, because the anæsthetist knows with much more certainty when the patient will come round. Short-acting substances are safer. The same is true of curarizing agents. The safest of these is succinylcholine which is so transient in its action that it is given in an intravenous drip. In both cases the preference for short-acting drugs is obviously sound.

But now the advocates of chlorpromazine have conveniently forgotten this experience and are using a substance which, when given, produces its full effect slowly, and of which the effect is unpredictably long. Surely it is not necessary to point out that there is a wide range of sensitiveness among different patients towards any drug, and that the use of a standard dosage of chlorpromazine will certainly have far greater effect in lowering temperature in some than in others. For these more sensitive patients there is no antidote, and all that the anæsthetist can do is to hope that they will not die. Whatever this position is, it is certainly not progress.

Conclusion

There are difficult and prolonged operations where the need to reduce post-operative shock is paramount, and where risks must be taken so far as the patient's later condition is concerned. There is evident agreement among anæsthetists who have used chlorpromazine that the signs of post-operative shock are very few. But even so the anæsthetist should, I think, bear in mind that little is yet known of the late effects of hypothermia induced by chlorpromazine. One may ask whether it is certain that there is no long-term effect on the patient's brain. Above all, nothing has been said about the effect of prolonged hypothermia on resistance to bacterial invasion. It is very difficult to believe that our past experience was all wrong, and that exposure to cold is a good thing. Are people who have been chilled to the point of a drop in body temperature really not in danger of serious infection, as we have always believed, and is that chilling less dangerous when it is achieved by

reducing metabolic processes with a drug? No doubt Time will supply the answer, and we may hope that we will get it without paying too high a price.

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Dr. D. A. B. Hopkin, Lambeth Hospital, London: The essential action of chlorpromazine lies in its action on the autonomic nervous system. Hypothermia is a secondary consideration. Laborit (1954) maintains that cooling benefits patients because it reduces cellular metabolism. Chlorpromazine permits cooling of semi-conscious patients before and after operation without bringing into action defence mechanisms against cold, which involve both the autonomic nervous system and the endocrine glands. Workers in this country (Smith and Fairer, 1953) and in France (Tardieu, 1954*a*) agree that all the advantages claimed for the use of chlorpromazine in anæsthesia can be obtained without resort to hypothermia.

Cathala and Pocidalo (1952) have shown that in animals chlorpromazine has a central action which besides including a degree of narcosis has a specific action in depressing the sympathetic centres of the mid-brain. Tardieu (1954*b*) maintains that this property is not possessed by any other sympatholytic drug.

Robertson (1954) has been able to demonstrate that chlorpromazine blocks sympathetic ganglia in low concentration. Further experiments showed that this differs from the block produced by methonium compounds. Clinical experience confirms this since marked vasodilatation and hypotension do not occur.

Jaulmes, Laborit, and Benitte (1952) have shown that both experimentally and clinically chlorpromazine confers protection against both traumatic and hæmorrhagic shock. The peripheral circulation appears to be stabilized. The small blood vessels and the capillaries appear to be impervious to either dilator or constrictor influences, and the circulatory changes which appear early in shock do not occur.

There is nothing new about sympatholytic drugs being of use in shock prevention. Such claims have been made for spinal analgesia, for methonium compounds, and for intravenous procaine. None of these have been an unqualified success because they lacked the central effect of chlorpromazine, and their action was not carried on sufficiently long into the post-operative period to allow the effects of trauma to die down.

The drugs with which Professor Burn classed promethazine and chlorpromazine all have a reputation for relieving bronchospasm, and prevention of post-operative pulmonary complications. Chlorpromazine is outstanding in this respect, and promethazine alone seems able to reduce the incidence of laryngospasm during anæsthesia.

There are therefore two good reasons for using them in anæsthesia: shock prevention, and reduction of post-operative pulmonary complications.

The experience of Dr. Bernard Kenton (Bethnal Green) and myself in over 500 patients fully confirms this. We have found the drugs of particular value in treatment of hæmorrhagic shock. They enable operation to be undertaken earlier, and massive blood transfusion is no longer necessary, and indeed can be dangerous. Two to three pints of blood are sufficient to restore full hæmoglobin value in severe hæmatemesis, when emergency gastrectomy is performed.

No toxic side-effects have been noticed. Occasionally post-operative tachycardia is observed. This settles within thirty-six hours. If delayed shock is seen it is probably due to too small a dose of chlorpromazine, since the maximum effect seems to wear off within five to six hours.

Our experience leads us to believe that these drugs have a real value in the prophylaxis and treatment of traumatic and operative shock, and can play an important part in prevention of post-operative morbidity, in particular that associated with pulmonary complications.

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Section of Medicine

President—Professor Sir HENRY COHEN, M.D., D.Sc., LL.D., F.R.C.P.

[*March* 23, 1954]

DISCUSSION: THE CLINICAL ASPECTS OF IMMUNITY

Professor A. A. Miles (Director, Lister Institute of Preventive Medicine, London) said that the term "specific immunity" usually meant "antibody immunity". The two factors to be considered were the capacity of the host to produce protective antibody, and the ability of the bacterial antigens to induce antibody formation. Bacteria contained many antigens, only a few of which were capable of inducing protective antibodies. The antibody-forming cells of the body had no powers of discrimination and were as likely to respond to the antigens of an invading organism that had nothing to do with protection as they were to produce a protective antibody.

It was difficult to separate relevant from irrelevant antigens for the production of vaccines, and to assess the results of immunization. A controlled clinical trial in a susceptible community would be the ideal test of a vaccine, but this had rarely been done. Vaccine had therefore to be devised largely on the basis of laboratory evidence, which was valuable in itself but required careful interpretation.

In diseases like diphtheria, immunity was very largely antitoxic, but in invasive diseases such as cholera, enteric fever and whooping cough the role of toxins was less certain. Resistance to endotoxins did not always confer protection against infection by the living organism. Endotoxins were often also surface antigens; in cases where anti-endotoxic antibodies had been shown to be protective the reason probably was that they were acting as opsonins, not as antitoxins.

In the case of the pneumococci the search for relevant immunizing antigens had been very successful. When virulent pneumococci lost their capsule they lost virulence, became useless as vaccines and susceptible to phagocytosis. Anti-capsular antibody was protective against infection and was clearly an opsonin. Another example of a non-toxic surface antigen largely determining protective immunity was the M-protein of *Str. pyogenes*. Although *H. pertussis* possessed several surface antigens, none had been conclusively proved by laboratory methods to be protective. The effective antigen had not yet been demonstrated with certainty by *in vitro* reactions.

In addition to toxins and surface antigens determining resistance to the host's defences bacteria may possess antigenic substances that appeared to be auxiliary pathogenic factors. These should not be accepted as important for artificial immunization unless there was evidence, not only that they were associated with the virulent form of the organism and had an observable effect on the host in conditions resembling those of natural infection, but that they were also capable of inducing protective antibodies. On this basis, for example, it would be difficult to assign any auxiliary pathogenic role to streptococcal hyaluronidase and fibrinolysin, because neither induces immunity against streptococcal infection.

Professor A. W. Downie, Dept. of Bacteriology, University of Liverpool:

Immunity to Viruses

I propose to confine my contribution mainly to the development of immunity in relation to the clinical course and recovery from virus infection. But by way of introduction a few general remarks on virus infection and immunity may not be irrelevant. Whether disease results from exposure to a virus depends on many factors relating to both the potential host and the virus. The susceptibility of the person exposed may be determined by non-specific factors as well as by the specific resistance largely dependent on antibody, which we call, in a rather restricted sense, immunity. Although the clinical picture is always influenced by susceptibility of the host, I do not propose to discuss this aspect of the matter at present. Of those viruses which may infect man there is a great variation in their capacity to produce disease.

1) Recent work with modern tissue-culture techniques has revealed the existence of a number of viruses hitherto unknown and perhaps not yet fully characterized. These have been isolated from tonsillar tissue and fæces. They produce degenerative changes in monkey tissues in culture and presumably multiply in the cells of the persons from whom they have been isolated; but as yet they have not been proved capable of producing disease. So far as we know, these viruses appear to be almost devoid of pathogenicity for man—infections appear to be always subclinical.

2) Recent work has proved, what was long suspected, that, in general, poliomyelitis virus is of relatively low virulence for man under conditions of natural exposure. For every case of paralytic poliomyelitis there are perhaps 50, 100 or even more persons who become infected but show no

clinical evidence of their infection. Most human beings are relatively insusceptible to clinical poliomyelitis or, in other words, the virus is of relatively low pathogenicity for man.

(3) Mumps virus is rather more pathogenic. The disease produced may not be serious but apparently 50% to 70% of all those exposed to the virus for the first time develop clinical signs and symptoms of infection.

(4) Of the more virulent viruses we might take those of measles and smallpox as examples. The virulence of measles virus was well illustrated by the epidemic in South Greenland in 1951 (Christensen *et al.*, 1953). There of a population of over 4,000 individuals exposed to measles virus for the first time less than 1% escaped disease. And in this country most people suffer from measles usually in childhood. In smallpox also, subclinical infection, if it exists, is rare in the absence of specific immunity, that is, in unvaccinated persons.

The immunity evoked by different viruses.—The immunity responses evoked by infection with viruses differ considerably. (There it may be noted that subclinical infection may induce an immunity response equal in kind and degree to that provoked by a clinical attack. The work of Paul and his colleagues (1952) has shown that the immunity of the population of Cairo to poliomyelitis is apparently due to the prevalence of subclinical infections in early childhood.)

(1) Some viruses are followed by immunity which is effective for many years. Such are most of those diseases in which there is generalized infection and the virus disseminated by the blood stream—for example smallpox, measles and mumps, in which one attack confers lifelong immunity.

(2) In a second group a clinical attack is followed by increased resistance for a relatively brief period, e.g. the common cold and influenza. In these diseases the infection is superficial, the virus being, we believe, confined to the cells of the respiratory mucosa; the relatively short duration of the immunity may be related to the fact that antibody in sufficient concentration cannot come fully into play, as Burnet (1950) and his colleagues have emphasized.

(3) In a third group of virus diseases, the immunity induced by an attack is of a relatively low order. Viruses of the psittacosis, lymphogranuloma group fall into this category. In psittacosis there is frequently a generalized infection but virus-neutralizing antibodies are difficult to demonstrate in the serum of the recovered patients, the virus tends to persist in the tissues and relapses have been recorded months afterwards. In lymphogranuloma venereum also there appears to be a poor or incomplete antibody response with persistence of infection.

The effectiveness of immunity following virus infection would appear, then, to depend on some inherent property of the virus which determines its antigenicity, and on the nature of the infection, particularly the degree or extent of tissue invasion by it.

There are perhaps two other points to which I might call attention before proceeding further.

(1) The immune response which follows virus infection is associated with the formation of antibody. Recovery from some illnesses appears to be determined by antibody.

(2) It is generally accepted that virus within cells is not affected by antibody. Antibody in blood or tissue fluids may therefore be effective against extracellular virus and may prevent infection of fresh cells but will not reach intracellular virus.

Antibody formation and the course of clinical illness.—In considering this aspect of immunity I propose to discuss two diseases, smallpox and poliomyelitis. Different kinds of antibody may be demonstrated in the blood following clinical disease but it is only with virus-neutralizing antibody that we are here concerned. In the two diseases that I have selected a good deal of information is available on the presence of neutralizing antibody during the course of clinical disease and after recovery.

Smallpox.—Although not a common disease, smallpox may serve as a model for other exanthematous fevers; because of the ease of handling the causal virus in the laboratory, the detection and estimation of antibody can readily be made. In smallpox the patient is acutely ill for several days before the rash appears. Soon after the appearance of the rash—from the third to the sixth day—the temperature returns to normal and the patient usually feels very much better. Later, in severe cases, there is secondary fever related to pustulation. The clinical improvement after the first few days coincides with and is probably due to the immunity response to the infection. Indeed antibody can be demonstrated in the serum of most patients at this time or soon afterwards. Of a number of sera from unvaccinated smallpox patients examined during the first ten days of the disease most had antibody by the fifth or sixth day of illness (Downie and McCarthy, 1954). Although some patients have a favourable course from this time onwards, the majority of deaths from variola major occur in the second week of illness or even later, after there has been an antibody response. Indeed several patients whose sera were examined died after antibody was present in their blood. These, and other severe smallpox cases, often have an increase in temperature and a stormy course during the pustular stage of the disease. This might seem to conflict with the idea that recovery from infection is largely determined by antibody. On the other hand the sequence of events is also influenced by the fact that, as previously noted, viruses inside cells are, by their situation, isolated from the action of antibody in blood or tissue fluids. Observations in Dr. F. O. MacCallum's laboratory and our own suggest that dissemination of virus by the blood stream occurs in most cases only for a short period, possibly

of h[illegible]s, at the beginning of the illness (Downie *et al.*, 1953). By the fifth day all cells in which virus is to[illegible]ow have already been infected. Even if antibody formation at this stage prevents infection of furth[illegible] cells virus increase in cells already infected may go on. In other words the outcome in smallpox [illegible] determined very largely by the extent of the viræmia at the beginning of the illness. And if the [illegible]ection of cells has been sufficiently widespread the resulting damage may prove fatal, in spite of th[illegible] presence of antibody.

Va[illegible]cination is generally accepted as an effective method of producing immunity against smallpox. Con[illegible]cts who have been vaccinated within the previous few years usually escape. Antibody capable of n[illegible]utralizing smallpox virus can usually be shown in the sera of such persons and indeed may be dem[illegible]nstrable in some twenty or thirty years after primary vaccination. But as one might expect, the [illegible]concentration and persistence of antibody following vaccination varies in different individuals. Those in whom antibody has disappeared may be susceptible to smallpox infection, although the dise[illegible]se is usually milder than in the unvaccinated. And these individuals usually have, as one might expect, a more rapid immunity response than the unvaccinated. In a number of sera from such cases antibody was not found in the first two days but was present by the third or fourth day of illness; that is to say the antibody response was apparently two or three days earlier than in smallpox patients who had never been vaccinated.

In such vaccinated persons as nurses exposed to heavy infection through contacts with patients in smallpox hospitals, presumably their serum antibody level is high enough, or their antibody response is sufficiently rapid to prevent the generalization of virus which is necessary before clinical illness can appear. *This means that antibody must be present within what would be the normal incubation period of the disease, if clinical illness is to be averted.* The result of passive immunization in the prevention of measles affords ample support for this view. Convalescent serum or gamma globulin containing antibody must be given in adequate amount before the fourth or fifth day after exposure, if measles is to be prevented.

Poliomyelitis.—Recent improvements in techniques for the study of poliomyelitis virus have made possible the rapid accumulation of immunological data; and here also our knowledge of the relation of the immunological response to clinical illness has extended. In the childhood type of clinical disease (Horstmann, 1949) there may be a minor illness accompanied by rise of temperature, headache or sore throat, anorexia and vomiting followed by a symptom-free period of two or three days before the paralytic phase sets in with headache, vomiting, stiffness and pain in the neck, back or limbs. The early temperature rise may appear without the subsequent paralytic illness and paralysis may occur in children and in adults who have not shown the early febrile episode. In the chimpanzee, which may suffer from clinical poliomyelitis after being given virus by mouth, the pathological and clinical features of the disease are comparable to what is seen in man. In the experimentally infected chimpanzee and in man, antibody can be found in the blood before the onset of paralysis; it usually increases in concentration during the next few weeks. In those few human infections in which viræmia has been demonstrated the examination of the blood has been made during a febrile illness in contacts, although in none of the children from whose blood virus was recovered did paralysis subsequently appear. However, the point that I wished to make is that, in some cases at any rate, antibody may be present in the blood just before the onset of paralysis. Paralysis is not prevented by such antibody because by the time the antibody appears virus is already present in the central nervous system. We know from the studies of Bodian (1952) and others on monkeys that histological evidence of damage to motor nerve cells in the spinal cord and medulla is apparent before clinical signs of such damage; and when paralysis has occurred the damage to nerve cells has been more extensive than the clinical evidence suggested.

It seems likely from the recent observations of Hammon and his colleagues (1952) that antibody has to be present before or soon after infection if clinical disease is to be prevented. The data from their trials of gamma globulin in the prevention of poliomyelitis showed that gamma globulin apparently gave some protection against poliomyelitis from the second to the fifth weeks after it was injected. But in the first week after injection the poliomyelitis incidence was no different in trial and control groups. Those who developed the disease within the first week after receiving gamma globulin were presumably in the incubation period of the disease at the time of injection and virus was perhaps already within nerve tissue before antibody was available in the tissue fluids. I understand that the American trials of γ globulin in 1953 gave little evidence of protective effect in those who received it, but I have not seen the figures and apparently the trials last year were conducted in a different manner.

In this discussion I have had in mind virus infection of an acute generalized nature—although there is not as yet evidence that all cases of poliomyelitis have a generalized infection in the sense of a viræmia at some stage of illness. It would appear obvious, however, that to prevent clinical disease from infections of this kind that antibody must be present in adequate concentration before the end of the normal incubation period following exposure. This can be achieved by active immunization before exposure, where a suitable vaccine is available, or by giving, parenterally, antibody in adequate amount soon after exposure. This latter method is likely to be valuable only in those

diseases with a relatively long incubation period. Practical experience of immunization methods is in accordance with these ideas.

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Professor B. Maegraith, Dean of the Liverpool School of Tropical Medicine:

Some Aspects of Immunity in Protozoal Infection

Immunity in protozoal infection may be natural or acquired. Natural immunity covers all forms of resistance to the parasite in the previously uninfected host. Acquired immunity embraces phenomena such as resistance to superinfection initiated by existing or past infection.

Natural immunity is generally considered to arise from properties inherent in the host or in the parasite. There is evidence, for instance, that resistance may sometimes run parallel to the physico-chemical environment of the host tissues or to the metabolic requirements of the parasite. Thus, invasion of red cells by *Plasmodia* is limited to certain groups of animals in which the erythrocyte potassium is high and sodium low; again, successful invasion of the host by certain trypanosomes can be correlated to the presence or otherwise of heavy metal catalysts in the parasites. It is sometimes difficult to assess the contribution of inherent factors to the resistance by a host to the initial parasitic invasion, since many so-called "natural" factors in resistance are probably largely governed by chance parasite-host relationships. An interesting example of this is the part played by age in determining the outcome of an invasion. For example, in certain hyperendemic areas human infants under the age of about three months are either not easily infected with malaria, or do not exhibit its clinical effects. How much is this governed by inherent resistant qualities in the infant and how much by extraneous factors? We have evidence that one of the factors involved in this suppression of malaria may be the breast milk. It has recently been shown that if potential hosts of malaria parasites are fed on an exclusive diet of milk, multiplication of parasites in the erythrocytes is checked. This suppression has been demonstrated in man (*P. vivax*), monkeys (*P. knowlesi* and *P. cynomolgi*) and rats and mice (*P. berghei*), and has been partly explained on the grounds that milk is deficient in p-aminobenzoic acid, addition of which to experimental milk diets or in large quantities to the diet of a lactating mother is followed by some restoration of parasitic development in the host. If it can be shown that the addition of p-aminobenzoic acid or the equivalent to the human mother's diet leads to a greater ease of establishment of infection in the infant, the indication will be that the age of the host in this case has little to do directly with the acceptance or otherwise of infection.

A similar lesson may be learned from the study of experimental amœbiasis. The acceptance of infection with *E. histolytica* by a host may be considerably affected by adventitious circumstances. For instance, the parasite can easily become established in a wide group of hosts in the contents of the lumen of the large intestine where the physico-chemical environment is suitable for its growth and multiplication. Establishment of the parasite in the gut of the same hosts, however, can be made much more difficult by changing the characteristics of the lumen contents by alteration of the host's diet. For instance, in dogs a milk diet tends to restrict the growth of amœbæ in the gut, whereas other diets (such as salmon) accelerate it. Invasion of the intestinal wall by amœbæ does not necessarily follow the establishment of multiplying parasites in the gut lumen. Many other things are involved, such as the numbers of parasites available and the ease of contact and the length of contact between parasite and epithelium. These factors and others similar may work together for or against ultimate invasion of the host. It is not certainly known how the *E. histolytica* cell penetrates the gut epithelium, but there is evidence that proteolytic enzymes are concerned. The presence of an inhibitor of these enzymes (such as serum) in the lumen contents can be shown experimentally to be important in the success or otherwise of an invasion. Similar considerations probably apply to invasion of the deeper tissues of the host. In this case it is reasonable to presume that the tissues normally exert a kind of negative resistance to the parasite, in that the conditions within them are unfavourable to its development. In the ordinary course of events, the parasites, stranded in such inhospitable surroundings, ultimately perish. Alteration in local conditions may, however, lead to parasitic multiplication. Thus, changes in local blood circulation or oxygenation may produce conditions suitable for growth. As will be seen, one factor of major importance in this

respect may be the establishment (as a result of existing or previous infection with the parasite) of tissue sensitivity states.

There is not the time to develop this subject. Inherent qualities are undoubtedly concerned in the resistance of a host to a given parasite. Nevertheless, in a given case it is unwise to accept resistance as a "natural" phenomenon in the sense of being inherent until the role of extraneous circumstances has been considered. The occasional successful infection of apparently resistant hosts with parasites not normally regarded as capable of infecting them, for example, the infection of rats with *Trypanosoma vivax*, emphasizes the point.

Acquired immunity to protozoal infections is probably developed in much the same way as in bacterial infections. In general, immunity arising from infection leads to resistance to further infection or to modification of existing infection. The existence of acquired resistance can be clearly demonstrated in many protozoal infections, for instance, in malaria in which past or current infection leads to the development of resistance to invasion by the homologous strain of *Plasmodium* but not by other strains, even of the same species. The factors involved in this resistance are similar to those concerned in similar circumstances in bacterial infections. They are evidenced by both humoral and cellular phenomena.

Infection with a given strain of, say, *P. vivax* in man leads in the course of two to three weeks to the appearance of agglutinating, complement-fixing and precipitating bodies in the blood, to changes in the surface charge of both parasitized and unparasitized cells, and to a form of phagocytosis. The latter is very specific for the particular strain of parasite and may be evident for months after radical cure of the prevailing infection; heterologous strains of the same species or other species of *Plasmodia* do not elicit it.

One of the important effects of acquired immunity in malaria is the modification of the clinical response to invasion. The acquirement of immunity leads to lessening of the host reaction to infection so that although it may not stop invasion or remove an existing infection, the clinical picture induced is usually much milder than would occur in a non-immune host. For this reason the practice has been established of considering patients infected with *P. vivax* (and other forms of malaria) in two groups: i.e., those with or expected to have acquired resistance, and those without it.

In these two groups the objects of treatment may differ. Acquired resistance is of considerable benefit to the individual living in an area where frequent reinfection is probable. In such instances, for example, in natives of an endemic area living in their own environment, treatment should be aimed at dealing with the immediate clinical attack. An attempt to eradicate the infection might lead, if successful, to loss of immunity and consequently to increased severity of clinical response in subsequent attacks. Treatment of the individual patient should therefore be concerned only with the erythrocytic infection which is responsible for the clinical attack. On the other hand, where the patient is intending to live outside the endemic area free from the possibility of reinfection, immunity is of secondary importance and the object of treatment changes. Eradication of infection now becomes desirable and the chemotherapeutic attack should be directed at both the erythrocytic parasites, which are responsible for the clinical attack, and the tissue forms (EE) which are responsible for subsequent relapses.

Details of treatment of *P. vivax* infection are thus: (i) For the individual with acquired resistance, and likely to be exposed to frequent reinfection: Any schizonticide in adequate dosage, such as quinine (grains xx for two days); Paludrine, mepacrine or chloroquine (500 mg. as a single dose). (ii) For the infected individual who has left the endemic area and is unlikely to be exposed to further infection: A schizonticide to deal with the blood infection, and an 8-amino-quinoline to deal with the tissue forms of the parasite. A common regime is: quinine, grains x; pamaquin (base) 8 to 10 mg.; given concurrently three times a day for ten days.

Passive immunity due to the existence of humoral bodies in the blood of an infected individual has been demonstrated in certain forms of malaria. Recently in berghei malaria in rats some evidence of transmission of immune bodies through the milk of the mother to the offspring at the breast has been obtained, which may account for some but not all of the protection of infants already mentioned.

One other point may be mentioned before this brief discussion closes. There is evidence that under certain conditions hypersensitivity to the invading parasite may develop in the infected host, and may influence the progress of the infection. It has recently been demonstrated, for instance, that sensitivity to certain extracts of *E. histolytica* cells develops in guinea-pigs with experimental intestinal amœbiasis. In sensitive animals, intraportal venous injection of *E. histolytica* leads to the establishment of persistent liver abscesses containing amœbæ; similar injection in the uninfected animals is followed by the production of transient hepatic abscesses which rapidly heal. The parasites thus appear to become established and persist more easily in the hepatic tissue of the sensitive host. One possible explanation is that in the latter antibody-antigen reactions in the liver are set up by metastatic amœbæ and lead to profound circulatory changes, thereby creating local conditions suitable for the growth and multiplication of the parasite, which becomes established and abscess results. Local circulatory changes can, in fact, be demonstrated in the liver following local intrahepatic injection of antigen in animals sensitized to horse serum. It is my belief that reactions of this sort may be of great importance in the development of invasion of host tissues by parasites, and that further study in this field would be richly rewarded.

[*April* 27, 1954]

DISCUSSION ON CHRONIC PYELONEPHRITIS

Professor M. L. Rosenheim:

Clinical Aspects

It is difficult for a clinician to open a discussion on a condition which only a pathologist can clearly define and diagnose. Pathologically the term "chronic pyelonephritis" is applied to kidneys which show irregular areas of scarring with characteristic histological features, the kidney often being reduced in size and its surface coarsely irregular. Histologically the scarred areas show hyalinization of glomeruli with periglomerular fibrosis, dilatation of tubules which characteristically contain pink staining colloid material, interstitial infiltration and fibrosis and often considerable vascular changes. These changes may be widespread throughout the kidney or there may be localized areas with relatively normal renal tissue interposed. The changes are readily recognizable and the diagnosis presents little difficulty on histological grounds. These features are, as Dr. De Navasquez will show, usually the end-result of inflammatory lesions in the kidney.

It is now generally believed that acute pyelonephritis is a blood-stream infection and that, before organisms appear in the urine, inflammatory changes occur in the kidney. It is probable that even the so-called ascending pyelonephritis complicating lower urinary tract obstruction with cystitis, is often the result of blood-stream spread. Most cases of acute pyelonephritis are coliform in origin and, in the vast majority, the infection of the urinary tract can be rapidly cured with, as far as we know, little subsequent trouble. In the presence of abnormalities of the urinary tract, congenital anomalies, hydronephrosis, calculi or underlying tuberculous infection, persistent or recurrent coliform infection is common. Even if the urine is not infected and, in fact, even if there is no clinical history suggestive of an acute pyelonephritis, scars of chronic pyelonephritis are commonly found in the kidneys of patients with such abnormalities. We are still uncertain whether an acute uncomplicated coliform pyelonephritis occurring in a previously healthy urinary tract ever leads to chronic pyelonephritis. It is probable that some underlying obstruction to urinary flow must also be present. Dr. De Navasquez has some fascinating experiments to describe which throw much light on this problem. I shall be particularly interested to hear whether he believes that infection must always play a part, or whether back-pressure alone may lead to the typical histological picture. I have in mind particularly those children with posterior urethral valves who insidiously develop renal failure.

Chronic pyelonephritis may be unilateral or bilateral. It may present with no obvious underlying cause or may be found complicating urological lesions. It is difficult to discuss the frequency of its occurrence, for the lesions and scars may be small and the observed incidence must vary with the care with which the search is made. The typical kidney of chronic pyelonephritis is small, with narrowed and irregular cortex and grossly scarred surface and the diagnosis can, on occasion, be made radiologically. It is worth noting that true chronic glomerulonephritis is always bilateral, of uniform distribution and symmetrical. If the kidneys are shown to differ in size, chronic pyelonephritis, rather than true nephritis is probably present. This raises the question whether the very small kidneys that are sometimes removed surgically on account of either pain, infection or hypertension, are primarily pyelonephritic or congenitally aplastic. It is probable that the true congenital aplastic kidney is often secondarily affected by chronic pyelonephritis and the distinction may be difficult to make. My experience is limited, but my impression is that hypertension does not occur as a complication of congenital renal aplasia unless the changes of chronic pyelonephritis are also present.

Under what clinical conditions may the presence of chronic pyelonephritis be suspected? It may be diagnosed in patients with chronic or recurrent urinary infection, it may be found as a cause of severe hypertension and is not infrequently responsible for the insidious onset of renal failure.

(1) *Chronic urinary infection.*—Recurrent or persistent urinary infection may be accompanied by the progressive renal scarring of chronic pyelonephritis, though I believe that this is not necessarily the case. A chronic cystitis or true pyelitis may occasionally persist for years with no evidence of renal involvement. The opposite also holds, that progressive chronic pyelonephritis may occur in the absence of history or clinical evidence of a chronic or recurrent urinary infection. However, the association of recurrent infection with secondary renal changes is sufficiently common to make the control of urinary infections a matter of great importance. If a urinary infection cannot be cured or if it recurs frequently, and if the underlying lesion cannot be corrected surgically, the infection should always be kept under control by regular chemotherapy.

(2) *Hypertension.*—Chronic pyelonephritis is a not uncommon cause of malignant hypertension. Many cases that previously might have been considered due to essential hypertension or chronic glomerulonephritis are now recognized to result from chronic pyelonephritis.

If the pyelonephritis is bilateral, the distinction from chronic nephritis or essential hypertension is of theoretical interest; but if unilateral, nephrectomy may cure the condition. In most cases of severe hypertension cured by nephrectomy the underlying lesion has been chronic pyelonephri is,

either simple or complicating some renal abnormality. I shall make only two points on hypertension due to unilateral renal disease:

(*a*) Only a relatively small area of one kidney may be affected.

(*b*) The damaged kidney may function quite well and show up on intravenous pyelography.

If total renal function is normal and if the sound kidney is normal in a patient with unilateral pyelonephritis and severe hypertension, nephrectomy is urgent and should not be deferred because the damaged kidney is still functioning.

We do not know why some patients with chronic pyelonephritis develop hypertension while others do not. Severe and widespread arteriolonecrosis may be found in those patients who have malignant hypertension, but in other cases, vascular lesions are limited to the scarred areas, suggesting some form of local arteritis.

(3) *Renal failure.*—Bilateral chronic pyelonephritis is a common cause of renal failure and, in the absence of a clear story of urinary infection, is often again mistaken for chronic glomerulonephritis. Uræmia may occur with or without hypertension, but insidious renal failure without hypertension is more commonly seen in chronic pyelonephritis than in true nephritis. Where hypertension coexists, progress of renal failure is rapid; where it is absent, the condition is usually only slowly progressive and there is often time for bizarre metabolic disturbances to occur. Chronic pyelonephritis may apparently lead to selective damage to the renal tubules. Impairment of the tubular ability to reabsorb certain ions is sometimes responsible for fascinating clinical syndromes, such as varieties of renal bone disease, episodic hypokalæmic weakness and paralysis and the "salt-losing nephritis" that may mimic Addison's disease. Occasionally an unexplained resistant anæmia is found to be the presenting sign of renal failure due to chronic pyelonephritis.

There is one other characteristic feature of the slowly progressive renal failure of chronic pyelonephritis—marked variation in the degree of failure from month to month. Wide fluctuations of the level of the blood urea may be related to recrudescence or remission of infection, to exacerbation of the obstructive element or to complicating factors such as excessive sodium loss. How far obstruction is primarily responsible for the renal failure in the individual case is always very difficult to determine, but obstructive lesions should, wherever possible, always be corrected.

How can chronic pyelonephritis be diagnosed clinically? There may be a history of past urinary infection and, in the patient who presents with hypertension or with renal failure, a history of recurrent urinary infection may be as significant as one of acute glomerulonephritis. Chronic pyelonephritis should be suspected in patients in whom severe hypertension is of recent or sudden onset, in patients with insidious renal failure with no hypertension and in those with recurrent urinary infections. It has been claimed that the presence of clumps of leucocytes in the urinary deposit, even in the absence of urinary infection, suggest an underlying chronic pyelonephritis, but I have not found urinary microscopy a valuable aid to diagnosis. Slight albuminuria may be present, but the urine is often entirely normal, with no albumin, no cells or casts and no growth on culture. This requires emphasis for urinary abnormalities are not essential for the diagnosis of chronic pyelonephritis. Urological investigation will often lead to the diagnosis, for unilateral renal disease and especially unilateral renal failure are often the result of chronic pyelonephritis, often secondary to some underlying abnormality of the urinary tract. Radiological appearances may lead to the correct diagnosis. As is so often the case, the diagnosis is much more frequently made when the possibility of its occurrence is borne in mind. Chronic pyelonephritis is one of several syndromes that have recently been separated out from the mixed bag of chronic Bright's disease. We must take care not to replace the loose term "chronic nephritis" with a similar indefinite clinical diagnosis of chronic pyelonephritis. The diagnosis can, and should, be made more precise; the presence or absence of underlying abnormality must be specified, we can try to decide whether the disease is unilateral or bilateral, and we can amplify the diagnosis by stating whether the condition is, or is not, complicated by the presence of renal failure or of hypertension.

Dr. S. De Navasquez:

Pathological Aspects of Chronic Pyelonephritis

There is now general agreement about the morphological features of chronic pyelonephritis which enable one to recognize and separate the condition from other renal diseases. These are asymmetrical contraction of the two kidneys, which is often very marked, associated with scars frequently coarse and giving rise to granular surfaces to which the capsules are adherent.

The microscopic appearances may vary in degree according to the age and distribution of the lesions but for the most part are characteristic. There are areas of replacement fibrosis roughly triangular in shape with the base attached to the capsule and the apex tapering towards the medulla and pelvis. These areas contain atrophied and fibrous glomeruli many of which are surrounded by fibrillary collagen which extends into the interstitial tissue. The tubules show various changes; some are atrophied and are reduced to small solid masses of epithelium while others are distended to cyst-like spaces containing eosinophilic—and therefore presumably protein-containing—clear fluid, surrounded by flat cubical epithelium and showing a superficial resemblance to thyroid tissue. These cyst-like tubules are considered to be typical of chronic pyelonephritis (Weiss and Parker, 1939)

and have not been seen in any other renal disease (Platt and Davson, 1950). In addition to these parenchymatous changes, there is usually a chronic inflammatory exudate of lymphocytes and plasma cells confined to the areas of fibrosis. The intervening renal tissue between the scars, when this is present, shows hypertrophy of the entire nephron. Bacteria are seldom demonstrable. Such is the morphological picture of chronic pyelonephritis. The pathogenesis is less well defined. One can reasonably assume on the clinical and pathological data that the final stages of the disease are represented by contracted granular kidneys and renal failure and that the greater the replacement fibrosis of the renal parenchyma, the older and more severe the disease, but these changes are only the end-results of a process which began with an original bacterial infection of the kidneys and which has progressed without revealing its precise evolution. Purely morphological studies (and there have been extensive since Bright's original description over 100 years ago) are not likely to shed further light. It is to the experimental method, which also has its own limitations, that we should turn for further knowledge.

The experimental methods I have used in producing chronic pyelonephritis have been described elsewhere (De Navasquez, 1950). A brief summary, however, is relevant to a consideration of the pathogenesis of this disease. Normal adult rabbits were injected intravenously with suitable doses of *Staphylococcus pyogenes* and many of them produced an acute pyelonephritis of limited duration with pyuria, pyrexia and an increased blood urea. A high proportion of animals survived from the infection and returned to apparently normal health and remained so for varying periods up to 2 to 3 years. During this time, however, some of the rabbits would begin to lose weight with increased blood urea and die. The urine would contain albumin but was sterile. The only lesion found post mortem was unequal contraction of the kidneys which showed coarse scars closely resembling those seen in human pyelonephritis. The histological similarities were even more striking. Areas of replacement fibrosis alternated with areas containing hypertrophied nephrons. Interstitial fibrosis with chronic inflammatory cells was present and cystic distension of tubules were a common feature.

So far, experiment has established that a bacterial infection of the kidneys can lead to the formation of scars without the persistence of bacteria which disappear spontaneously after producing suppuration. Furthermore, such a transient infection may initiate changes in the nephrons which are progressive and which may terminate in renal failure after a considerable lapse of time. Microscopic examination by serial section reveals a constant finding, which is the presence of scars which interrupt the continuity of the nephrons at many levels. The mechanical consequences of such fibrous strictures in the ducts of an excretory organ are familiar and readily seen in the hydronephrotic ureter. The tubules are part of the same tubular system which begins at the glomerulus and ends at the urethra and are therefore liable to the same mechanical effects of obstruction and I believe that the cystic dilatation of the tubules seen in pyelonephritis represent what one might term an "intrarenal hydronephrosis". There is, however, a complicating factor in that such hydronephrotic tubules are closely intertwined with surviving and hypertrophied nephrons which probably interfere with the normal pressure gradients and which may limit their distensibility according to the level in the nephrons at which obstruction occurs. Although these mechanical considerations may reasonably account for the morphological picture, they appear to be inadequate in explaining the progressive diminution in function, leading eventually to renal failure.

During the course of experiments still in progress, it was found that rabbits with kidneys scarred by past pyelonephritis but secreting a sterile urine, were much more liable to reinfection of the kidneys from bacteria circulating in the blood, either when introduced artificially by intravenous injection or during the course of a naturally acquired infection. The mechanism which determines the localization of bacteria in scarred kidneys is still being investigated but it is thought that slowing of the blood stream in the granulation tissue of the scars and in atrophied nephrons is a likely factor, as this would allow time for micro-organisms to multiply to sufficient numbers to produce a suppurative lesion. Recurrent infection is clearly an additional factor which, by destroying more nephrons and causing replacement fibrosis will lead to further reduction in functional capacity. Such infections are usually transient and may well escape clinical notice, hence the almost invariable absence of demonstrable bacteria either in the kidneys or urine of chronic pyelonephritis in man. It is tempting to believe that a spreading suppurative lesion affecting any area of the kidney will sooner or later involve patent nephrons in the vicinity and thus discharge its contents of pus and bacteria into natural channels where they are drained by the flow of urine, thus limiting the duration of the infection.

Though the contraction of the kidneys and diminished renal function may reasonably be attributed to atrophy and replacement fibrosis affecting part or whole of a few or many nephrons, the diverse clinical syndromes which may be seen in chronic pyelonephritis cannot be explained on a purely quantitative basis. Oliver (1944–45) has shown by microdissection of nephrons in contracted kidneys, the great variety of malformations which may occur. The apparently haphazard distribution of aglomerular nephrons, blind or shortened patent tubules must surely affect the functional capacity, both quantitatively and qualitatively. The nephron is rightly considered to be the functional unit of the kidneys but its constituent parts of glomerulus, convoluted tubules, ascending and descending loops have different functions within the unit and may not the different biochemical effects such as loss of electrolytes seen in some and not other cases of pyelonephritis be related to a preponderant

loss of one or other component of the nephron? The answer must wait until such time when we will be able to assess separately the functions of these different components and which will also enable us to estimate the powers of regeneration, hypertrophy and adaptation of each part.

So far we have considered chronic pyelonephritis as a distinct pathological entity, the evolution of which depends on the following consecutive events:

(1) Hæmatogenous infection.
(2) Acute pyelonephritis (Primary; staphylococcal).
(3) Organization and replacement fibrosis.
(4) Intrarenal hydronephrosis.
(5) Recurrent pyelonephritis (Secondary; coliform).
(6) Chronic pyelonephritis.

When these events occur in both kidneys which are free from extrarenal obstruction such as hydroureter, the resultant pyelonephritis presents naturally as a medical disease, but is there, in fact, any difference beyond one of degree, between the localized changes seen in part or whole of one kidney affected by obstruction of the ureter by, say, a stricture or calculus, which is seen mainly in surgical practice? I find it very difficult, if not impossible, to distinguish between the histological features of the scar proximal to a surgical lesion such as calculus or tuberculous focus and that seen in the kidneys of bilateral chronic pyelonephritis. We accept hæmatogenous infection in extrarenal hydronephrosis, it seems reasonable to do so likewise in the miniature hydronephrosis within the kidney. The mechanical consequences are similar in both, varying only in degree, extrarenal obstruction affecting the whole kidney, intrarenal obstruction affecting only that part of the nephron proximal to the obstruction and depending on the level of the nephron at which it occurs and its extent, whether diffuse or focal, will determine the more varied picture seen in chronic pyelonephritis.

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Dr. J. M. Stansfeld:

Chronic Pyelonephritis in Children

Pyelonephritis is relatively common in childhood. It is difficult to ascertain its true incidence amongst the unselected child population but I have some data from the 1,000 families survey at present being carried out at Newcastle.[1]

There were 847 children who were closely watched throughout the first five years of life and in that time 4 of them developed pyelonephritis. That incidence of 4 in 847 compares with 5 cases of pyogenic meningitis, 4 of intussusception and 3 of pyloric stenosis. In this sample, then, these diseases all occurred with about equal frequency but their response to treatment and duration in hospital was very different. The cases of meningitis and so on were only in hospital for a week or two whereas those with pyelonephritis were all repeatedly admitted and spent an average of a month there altogether. Pyelonephritis, in fact, accounts for many of the admissions of children to hospital. During the past four years, excluding those children admitted for removal of tonsils and adenoids, there have been an average of 14 cases for every 1,000 children admitted to hospitals in the Newcastle area. That represents quite a large problem, especially as 60% of the cases were chronic, necessitating long stays in hospital.

If now the incidence of pyelonephritis in children is studied more closely two significant features stand out. Firstly, the disease is more common in females and secondly, it particularly affects the younger age groups. The sex difference is, of course, well known but it does not hold so much for the younger age groups when the female dominance is not nearly so marked. In infancy the female preponderance is less than 2 to 1 whereas in those who start the disease after the first year of life the ratio is nearly 9 to 1. Indeed it is relatively uncommon after infancy for boys to contract the disease.

Turning to the age incidence, Fig. 1 shows the age of onset of symptoms in 156 cases and demonstrates how much more frequently pyelonephritis begins in the first year of life than at any other time.

If pyelonephritis occurs fairly frequently in childhood and if infants particularly are its victims, one would expect that familiarity with the condition would lead to its ready recognition in this age group. Unfortunately this is not the case and, in my experience, the disease is hardly ever diagnosed by the family doctor or at the Child Welfare Clinic. It is a striking fact that in a series of 85 cases under 2 years of age only once was disease of the renal tract even suspected before reaching hospital. Although some untreated cases may recover spontaneously, in many the consequences of missing the diagnosis and so not giving adequate treatment are serious and the infection smoulders on relentlessly.

[1] Unpublished data (1954) from a survey under the direction of Sir James Spence, Dr. F. J. W. Miller and Dr. Stanley Walton.

In these, chronic ill-health or recurrent febrile illnesses may continue throughout childhood and there is evidence that some may die of renal failure, with or without hypertension, in adolescence or early adult life.

It is tragic that such end-results should occur so frequently when, at its onset, the disease is readily curable.

There seem to be three main reasons why in infants the condition is often overlooked:

(1) Symptoms are gastro-intestinal rather than related to the renal tract.
(2) The physical signs are scanty.
(3) The pyuria may be difficult to demonstrate.

I would like to consider these in turn.

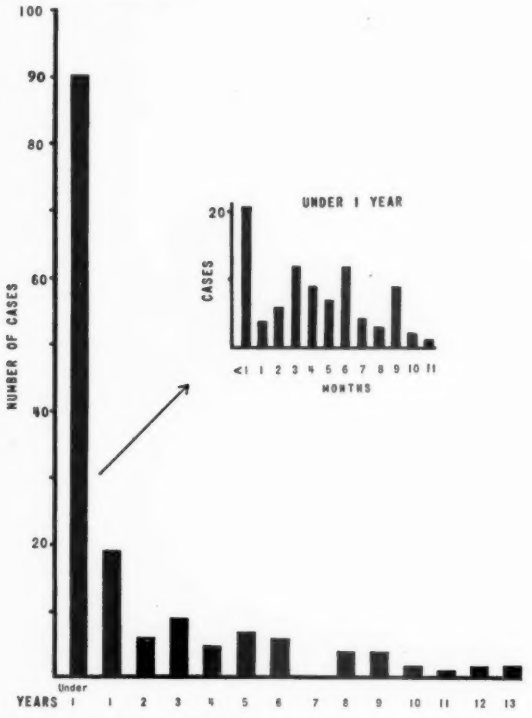

FIG. 1.—Age of onset of symptoms in 156 cases of pyelonephritis in children. Inset shows analysis of cases in those under 1 year.

There is a tendency to think of pyelonephritis in infants only as it presents in the acute form. Descriptions since the classical one of Holt in 1894 have emphasized the dramatic nature of the illness with a sudden onset, marked fever, prostration and often rigors or convulsions. Yet the majority of cases start insidiously and become chronic. There is a gradual failure to thrive rather than any dramatic upset. For no obvious reason the child goes off his food, perhaps vomits occasionally, becomes fretful and constipated yet shows very little on physical examination. The diagnosis is then missed, not because of any lack of symptoms or because the doctor is not consulted but rather because the disease is not called to mind. This is understandable, for in infants, in contrast to older children, symptoms directly referable to the renal tract are not usually evident. The baby normally is wet most of the time so that frequency may not be obvious; he cannot complain of pain or burning on micturition and his urine, which soaks into the napkin, is not readily observed either by the mother or the doctor.

Nevertheless, the clinical picture is distinctive and surprisingly consistent. Table I gives the incidence of symptoms and it will be seen how those of the gastro-intestinal tract predominate. Anorexia is practically invariable, solids in particular being refused. Vomiting is almost as characteristic and often occurs in bouts. These two symptoms—anorexia and vomiting—lead to both constipation and a failure to gain weight. In addition, although some babies with pyelonephritis

are g[illegible]d and placid throughout their illness, in the majority fretfulness is a striking feature—there being [illegible]l grades from just misery when the bottle is presented, to actual screaming attacks as if in pain. [illegible]able I also shows that in spite of what I have just stated many do have symptoms related to m[illegible]urition, especially frequency or a smelly urine, but the point is that these have to be asked abou[illegible]nd and are rarely volunteered by the mother. Finally only a few cases have convulsions which are th[illegible]s not particularly characteristic of pyelonephritis.

TABLE I.—FREQUENCY OF MAIN SYMPTOMS OF CHRONIC PYELONEPHRITIS IN INFANCY (59 CASES)

Symptom	% occurrence
Anorexia	96
Vomiting	88
Failure to gain weight	75
Irritability or screaming attacks	66
Constipation	61
Micturition symptoms*	45
Smelly urine	37
Thirst	34
Apathy or drowsiness	10
Diarrhœa	10
Œdema	5
Convulsions	3

*These include frequency of micturition in 32%, dysuria in 12%, and periods of anuria in 8%.

In spite of the number and prominence of the symptoms of pyelonephritis in infancy, physical examination usually reveals surprisingly little and one may be tempted to think the mother's anxiety is unwarranted. It is only the severe cases with relatively long histories that look really ill and have sallow complexions with pallor and marked wasting.

In infants then the diagnosis of pyelonephritis is chiefly suspected on the history, and the moral is that the urine should be examined in any infant with unexplained anorexia, bouts of vomiting or loss of weight.

This brings me to my main point. Confirmation of the diagnosis of pyelonephritis depends upon the demonstration of pyuria. The bacteriology of catheter specimens of urine may support the diagnosis but, because contamination can occur so readily, it cannot form its basis. Now the pyuria, at any rate of chronic pyelonephritis, may only be intermittent and then only modest in amount. The intermittency is a well-known fact and one of the best demonstrations of it was by Geisinger (1931). Obviously the diagnosis of pyelonephritis cannot be ruled out on the finding of one or two normal urines and in a suspected case repeated specimens may need to be tested.

The pyuria may be only very slight and it is essential to recognize the difference between a high normal excretion of leucocytes in the urine and a low-grade but significant pyuria. This is not always possible using the customary method of counting cells per high- or low-power microscope field. For one thing there does not seem to be agreement in interpreting results when only a few cells are present and opinions differ as to how many cells may normally be found. Some accept up to 6 or 8 cells in each high-power field and others do not think that there should be more than 1 or 2 in a low-power field—a considerable difference. Then, of greater importance, the method is so haphazard and crude that it will only detect relatively gross amounts of pyuria.

We in Newcastle have adopted the routine of counting the number of pus cells in a cubic millimetre of [illegible]rine using a counting chamber. The procedure takes no more time than the microscope field co[illegible]nt. It seems a perfectly logical thing to do for the cell content of other fluids such as the cerebro-spi[illegible]al fluid or the blood are measured with remarkable accuracy and no one would think of rep[illegible]rting on unmeasured samples. The advantages of doing an accurate urine cell count are en[illegible]mous. Not only is the method more precise but, and this is the crux of the matter, since a far lar[illegible]r volume of urine is examined slight but significant pyuria is revealed which otherwise would be [illegible]issed. The results are easily interpreted. One needs to know what are the limits of normal ex[illegible]etion and we have found (Stansfeld and Webb, 1953) that in boys of all ages and in infants of eit[illegible]r sex urines mostly contain under 10 cells per cubic millimetre and over 50 cells are rarely found in [illegible]e absence of renal tract disease. Girls have the same in their catheter urines but, after infancy, th[illegible]e naturally voided may be contaminated and up to 500 cells may be found. These figures are fai[illegible]y precise, but it is difficult to correlate them with microscope-field counts as the latter vary so m[illegible]h according to the size of the drop of urine held by the coverslip. However, very approximately, an [illegible]verage of one cell in each high power microscope field is equivalent to some 250–500 cells per

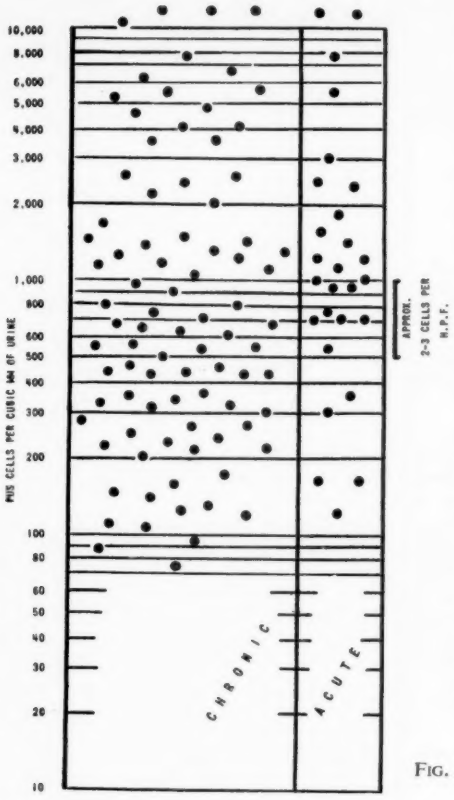

FIG. 2.—Maximum pyuria in 115 cases of pyelonephritis.

c.mm. In other words except in girls over a year old an average of more than one cell in 10 high-power fields seldom occurs under normal conditions.

Turning now to the urine cell count findings in cases of pyelonephritis, Fig. 2 shows the maximum counts found in 115 cases. The maximum urine cell count for each case is shown by a dot. There is a great variation in counts. In some the urine is thick with pus which is easily detected whatever the method, but such cases are by no means the majority and about as many have only small amounts. The approximate level of 2–3 cells per high-power field is shown and if this figure had been accepted as normal then a large number of cases would have been overlooked.

There is yet another advantage of measuring pyuria by the counting chamber method. Being a more sensitive technique, pyuria in cases of pyelonephritis can usually be disclosed by examining just one or two specimens and one rarely has to look at repeated urines. Table II illustrates this by showing just how many urines were needed for diagnostic purposes in a series of cases. In acute cases never more than two specimens were required. In chronic cases, although sometimes many urines needed to be looked at, in by far the majority the first specimen to be examined was revealing.

TABLE II

NUMBER OF URINE SPECIMENS TESTED IN ORDER TO DISCLOSE SIGNIFICANT PYURIA IN EACH OF 136 CASES OF PYELONEPHRITIS IN CHILDREN

Diagnostic specimen of urine	1st	2nd	3rd	4th	5th	6th	7th	10th	11th	17th	19th
Number of acute cases ..	36	2	—	—	—	—	—	—	—	—	—
Number of chronic cases ..	68	10	5	2	3	4	1	1	2	1	1

Treatment of pyelonephritis in children.—This is not always easy and, apart from those having an anatomical lesion in the renal tract, the treatment of the chronic case is a long and hazardous affair. The longer the history the worse the results. 34 cases who had a history of four months or longer averaged three hospital admissions each. It does not seem to be a question of just sterilizing the urine—that is usually easy—the difficulty is to eradicate the infection from the interstitial tissues of the kidney, for unless this is done relapses will occur. For this reason it seems to be a mistaken policy to give smaller doses than usual of drugs because of their concentration in the urine. It is the level of antibiotic in the kidney tissues rather than in the urine that matters. Even when full dosage of drugs is given a prolonged course of treatment is needed. Therapy should go on sufficiently long to allow the kidney tissue to become repaired otherwise reinfection or relapse is liable to occur (Stansfeld and Webb, 1954).

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Section of Psychiatry

President—E. B. STRAUSS, M.A., D.M., F.R.C.P.

[*January* 12, 1954]

SYMPOSIUM ON PSYCHOPATHY [*Abridged*]

Professor Alexander Kennedy:

Psychopathy and Social Responsibility

Psychopathic personality is as often manifested as a disorder of citizenship as of personal adjustment and some clarification of our ideas about its nature is necessary if we are to present the problem of the misfit, for whom society can find no place and science as yet no remedy, to the social agencies who discover him as a hindrance to any activity in which planned co-operation is essential. In the case of some psychopaths it is helpful to regard the condition as a defect-state in which the mental apparatus necessary for interchange between the individual and the group is, due to structural defect or failure of development, not as efficient as his cognitive abilities.

In certain psychopaths the mechanism for monitoring or controlling behaviour appears to be absent or inefficient, leading to unpredictability, impulsive behaviour and emotional overflow. This defect is rarely complete but it is sufficient to render difficult the integration of the different aspects of the individual's personality so that he adapts at a different level in respect of each quality of personality. The painter, for instance, who adapts at one level of artistic integrity and at a very different level of sexual or financial morality is a psychopath if he or others suffer as a result. On the other hand, the mental defective who also lacks financial morality is not a psychopath because his adaptation in this respect is consistent with his expected efficiency in other spheres. This disparity of the different qualities of personality is very characteristic of the psychopath.

A feature of the psychopath with poor social adaptation is his lack of foresight, a process in which the monitoring of behaviour is projected into the future. It is dependent on a state of *conative awareness* (Jefferson *et al.*, 1950). Any contemplated course of conduct must be monitored not only for immediate expediency, but for compatibility with the general attitudes and trends of the individual, as installed in the great reference library of the brain, laid down in the formative years of life. Training and early experience thus lay down the codes and attitudes by which later conduct is guided, and in this lies the importance of infantile experience and of the first contacts made with parents, with the family and finally with society itself. This *personal codification* of the principles learned from early experience has, as the psychoanalysts have shown, an immense determining influence on later conduct. If, however, the mechanism for monitoring or reality-testing is deficient or undeveloped the individual has a greatly diminished chance of keeping in step and is dependent on the sort of crude defence mechanisms and compensations which are a feature of adaptation and the severe neurotic. Crude neurotic mechanisms are thus a common feature of the psychopathic personality.

Partial defects of understanding also play their part. Just as the word-blind or arithmetically-disabled child can be helped by modified education, so the psychopath can sometimes be helped, if the nature of his disability is understood. The intelligent child who cannot do arithmetic is an example of such a partial defect. By the time the defect is discovered the child may be presenting alarming evidence of hatred of the school and all its works, of which failure to succeed at mathematics may well be taken for a symptom, and not the cause. This has its counterpart in the psychopath who, unable to understand how he differs from the rest of mankind, is likely to rationalize, to invent his own reasons for his difficulty, and to turn against the society with which he cannot make any satisfying contact.

The diagnosis of psychopathy is usually made by a process of progressive restriction, by reviewing the things that the patient is not. The following list includes the salient features in the sphere of social adaptation.

Their behaviour mystifies others who find it difficult to account for it in terms of their own motives. Their solution of daily problems differs from that of the average man of comparable intellect, yet they are lacking in insight as to the ways in which they differ from others. Their output is irregular and unpredictable and their response to alcohol and drugs is unusual. Owing to their disability they attempt to meet stress in inefficient ways and are in consequence vulnerable to neurosis. They have difficulty in keeping their attention on the

immediate need for adaptation to daily life. On the other hand they may be preoccupied with the present alone and incapable of considering the future. They are often egocentric and can find no reason for any other attitude. They are sometimes criminal and share with the criminal the weakness for accepting the immediate gain with restricted foresight for later consequences. They are not insane, but cause more unhappiness and disharmony in others than the insane. This unhappiness they are unable to appreciate. Out of place in this world, they may seek to reform it by new politics or religions, or to leave it by suicide. Their emotional responses are at the extreme of the normal, they cannot estimate their appropriateness or respond consistently to the same situations at different times.

The descriptive stage of enquiry into psychopathy has already been most admirably carried out, not only by clinical workers but in literature generally. The time has now come to test hypotheses in the hope of reaching a unifying theory. To the question "Can we make a psychopath experimentally?" there is at least a partial answer in the study of the late effects of encephalitis lethargica and of the after-effects of brain-damage. The lack of foresight found in the brain-damaged appears to be due to a general lack of awareness in the conative field which accounts for some of the extraordinary unforesightful acts which are sometimes seen in the presence of an otherwise normal intellect. They occur where the disease has been incident at the stage when a child is learning to avoid danger. In the same way, socially unforesightful acts occur in those where it has been incident between the ages 8 and 20 when the sense of social responsibility is undergoing rapid development. The man of normal test-intelligence who kills a man for his new suit and leaves his old one at the scene of the crime, is a striking example of this sort of defect. The type of moral defect seen in the post-encephalitic and in the patient with gross character change after brain-damage are very different, and it is possible to isolate the factors they have in common and in which they differ (Jefferson *et al.*, 1950). They serve, however, to illustrate the fact that it is possible by means of comparatively small structural damage, or by interfering at critical phases of development, to produce an individual who *lacks the physical means of being morally aware.*

Between conception and maturity there are many opportunities for minor damage to the nervous system, especially in view of the high survival rate in those with minor congenital anomalies, after extreme prematurity, severe birth injury or central nervous disease in early life. Many of the defects may only come to light when the affected mechanism is tested under the stress of adolescence. Nor can heredity be ignored as there is sound recent evidence that the inheritance of abnormal character traits is at least as clear as that of psychiatric disease entities. It is certain, however, that not all psychopathy is due to defect-states for, however perfect the structure, there must be normal opportunities for the development of character. As the structure of the group in which we live becomes more complex and as it becomes more necessary to make laws, and especially regulations, on the assumption of a conforming attitude in each individual, the number of those who will be unable to subscribe to the spirit of them is likely to increase. It is unfortunate that the Welfare State can be to some only an incitement to exploitation and we are in danger of testing the citizenship of some of our population too far. The law, in particular, has constantly to deal with individuals for whom at present it has little provision. We can no longer deport our misfits and we cannot destroy them. We know that punishment cannot alter the basic condition, although there is reason to believe that with specially devised and realistic sanctions such individuals can be made reasonably happy and can approach self-support. At present we remove from the community those only with intellectual defect, those who are criminal yet manifestly not responsible for their crimes, those who are dangerous, and those who have repeated in crime so often that all hope of reformation must be given up. We must find means, if they fail in a therapeutic environment, to plan a satisfying life for these incomplete human beings in whom our laws and customs give rise only to perplexity and frustration. To retain them as citizens of whom the normal duties are to be expected may often only add to their burden. The provision of a suitable but separate non-penal environment for those subjects who are lacking in the qualities essential for citizenship in an overcrowded world is essential if the march of civilization is not to be held back to the pace of its stragglers.

[This paper will appear *in extenso* in *J. ment. Sci.*]

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Dr. Maxwell S. Jones:

The Treatment of Psychopathic Personalities in a Therapeutic Community

The social rehabilitation unit at Belmont Hospital[1] was started almost seven years ago and has 100 beds primarily for the treatment of character disorders of both sexes. The aim of the unit is to subject the antisocial individual to a socializing experience which may lead to some modifications in his behaviour and lessening of his social tensions and also help him to get greater satisfaction from his social relationships.

[1]Belmont Hospital is a neurosis centre which includes the Social Rehabilitation unit. Dr. Louis Minski, the Physician Superintendent, has been most helpful to us in developing this experiment.

The cases admitted to the unit may be referred by psychiatrists, from the Courts, or the Employment Exchanges in any part of the Country, and they stay in the unit with us for up to twelve months.

We have tried to develop a community which aims constantly to study and modify its own tensions, values, aims and social organization with a view to the education and treatment of the psychopathic patients. In order to do this the patients and staff must learn to communicate freely with each other and amongst themselves. This has led to the establishment of numerous group (less than twelve people) and community (more than twelve people) meetings. At the present the entire patient and staff population meet daily for an hour and each of the four psychiatrists on the unit spends approximately five hours daily in group and community meetings and only three hours daily on individual interviews. The pressure to communicate in order to obtain some relief of tension and to participate in the varied social life of the unit is much stronger than is found in the ordinary hospital, or in domestic and work situations.

How does a therapeutic community such as this produce change in the social attitudes and values of many of the patients? We know that such changes do occur as is shown by a careful follow-up study (Jones, 1952).

There seem to be fluctuations in the overall social climate. The discharge of a group of patients who have become acculturated during a stay of several months may result in considerable social disorganization especially when the new admissions who replace them have strong aggressive and anti-social trends. The tensions in the patient and staff population may rise and the community seems to get progressively more disorganized. Every patient attends several community meetings and at least one therapeutic group every day so that these tensions will be discussed and analysed and in the process the meaning of the antisocial behaviour becomes better understood. Frequently a split appears between the older patients and the new patients and some of the older patients may regress to former patterns of antisocial behaviour. The anxiety and lack of security may lead the older patients to join in the criticism of the staff by the newer patients. Why is there no treatment, why do the staff *do* nothing to correct the disturbed state of the wards after lights out, the food which was praised a few weeks previously now comes in for bitter attack, and so on. The threat of disintegration seems to lead to a need for reintegration just as seems to have happened in so many of the P.O.W. camps when the initial survival of the fittest and disappearance of a social conscience was later replaced by a higher sense of social responsibility than had existed in civil life (Curle and Trist, 1947). A somewhat similar motivation seems to be behind some of the reparative functions of Alcoholics Anonymous; alcoholics find themselves slowly cut off from their families and friends and are then helped back to health by sharing in a community experience with people who understand them, and help them to learn new social values.

It would seem that psychopaths more than any other type of psychiatric casualty need an opportunity to learn to establish good social relations. In many ways they behave like infants of 2½ years and have not yet come to terms with reality. They cannot delay satisfaction of their instinctual needs and show little or no capacity to make friends or consider the feelings of other people. Inevitably their aggressive behaviour tends to arouse resentment among their fellows and frequently they appear to try and invoke such rebuffs in order to ally their feelings of guilt; by establishing the idea of unjust treatment they attempt to rationalize their revengeful sadistic attitudes. The absence of understanding and security in the early parental relationships has usually resulted in a relatively undeveloped social conscience. We believe that even with adult psychopaths much can be done to produce personality growth. In the unit we have no manifest authority but all problems are referred back to the community. This means that the result of the psychopath's impulsive behaviour is constantly brought to the notice of the individual patient and of the community. Threats of suicide, actual attempts, aggressive behaviour, drunkenness, &c., are all common topics for discussion and are brought into realistic perspective by the other patients and staff who do not hesitate to emphasize the anxiety which such behaviour provokes in other people. The absence of any punitive attitude, however, offers reassurance to the psychopath who is rather bewildered by the failure of the community to respond in the familiar revengeful way. Moreover his own aggressive needs are not met. It is not uncommon to hear the psychopath suddenly exclaim in a community meeting something like, "I never realized before how much my outbursts were upsetting other people". We believe that in such a setting (particularly after a period of destructiveness by the community followed by a reparative phase as already described) the inhibited personality growth may now continue. Better social relationships may be established with the staff or other patients and the patient may now show his willingness to accept one of the innumerable socially valuable roles which are afforded in a therapeutic community. The patient in an ordinary hospital is offered little opportunity to use his initiative or to be useful. He is expected to show an almost childlike dependence on the hospital and accept without question the role assigned to him. We suggest that by elevating the status of patients to that of active participants in a therapeutic community the psychopath at least is given an opportunity to learn and increase his capacity to establish social relationships. Moreover he may begin to substitute more constructive endeavour for his previously impulsive behaviour. Along with these changes we frequently observe an increasing concern about the upset which antisocial

behaviour causes the community. The pleasure which the psychopath appeared to derive from his previous aggressive or sadistic behaviour is now replaced by growing feelings of guilt. The patient begins to identify himself with the aims of the unit and a suitable role for him at this stage is to be invited to serve on the reception committee of older patients who introduce new patients to the unit during the first few days of their stay.

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Dr. Edward Glover:

The Ætiology and Classification of the Psychopathies

To place psychopathy in a systematic classification of mental disorders and to discover suitable ætiological formulæ for the group of conditions require common agreement on psychiatric definitions, an agreed outline of mental development and a clinical consensus of opinion regarding the ætiology of collateral types of disorder. This agreement depends in turn on recognition of the unconscious factors contributing to normal and abnormal development. Regarded from the standpoint of normal psychology, we require accurate definitions of "character" and indications of the normal range of sexual and aggressive impulses. Psychopathy comprises disorders of character, emotional instability, incapacity to control instinctual discharge, disregard of consequences, apparent absence of remorse, and usually a number of abnormal psycho-sexual manifestations.

There are also social criteria set by the community at large and, since a good deal of psychopathic aggression is directed against the family, also by familial codes of conduct. Moreover, under war conditions quite normal persons are required to behave on occasion like homicidal psychopaths. And since many advanced psychopaths are frequently mistaken for normal persons, we may expect psychopathy to have as many affinities with "normality" as with mental disorder.

There are, in fact, not many resemblances between psychopathy and the neuroses, since in the neurotic person the impulses, which in the case of the psychopath are given open expression, give rise to unconscious conflict and are therefore inhibited. The psychopath, however, often suffers from states of confusion before a crisis similar to those found in the neuroses. And the compulsive nature of psychopathic conduct has some resemblances to the reactions of obsessional neurotics. The ego of the neurotic is, however, comparatively free from disorder, whereas in the psychopath the ego is profoundly disturbed.

Comparing psychopathies with the psychoses we find in the former many of the projective manifestations seen in schizophrenia and paranoia and in the schizoid and paranoid character. The reality sense of the psychopath shows a defect in range and in appreciation of consequences similar to that found in the psychoses. Nevertheless psychopathies must be distinguished from the psychoses. Ætiologically regarded they have some correspondences with transitional states such as alcoholism and drug addiction, particularly the paranoid types of alcoholism. Nevertheless the ego of the alcoholic during remissions is not psychopathic. Two guiding rules should govern any attempt to delimit psychopathy: (1) when a disordered state can be better placed in another category it should not be included under psychopathy; (2) when during remissions the ego is found to be normal, the state is not psychopathic. Suicide, for example, is better classified under the depressions: alcoholism should remain a self-contained group: compulsive conduct is better labelled obsessive and aggressive inferiority is often a pseudo-hysterical manifestation. Schizoid characters are, however, difficult to distinguish from psychopathies. Psychopathic manifestations have usually persisted without interruption from early childhood—a useful differential characteristic. We can also exclude from the group all cases of sexual deviation and perversion in which a relatively intact ego exists, a state of affairs which may be found even in the sadistic perversions.

The structure and function of psychopathy are best established by distinguishing respectively: (a) *constitutional*, (b) *developmental predispositional*, and (c) *precipitating* factors. Constitutional factors include variations in instinctual stress and in need for gratification, or incapacity to stand frustration. The earliest stages of mental development are essentially traumatic and in psychopathy there are signs of an incapacity to stand even minor stresses. Exacerbations of psychopathy also tend to occur at various periods of psycho-biological stress—puberty, mid-adolescence and the early twenties. An unconscious homosexual factor usually contributes to this stress. It is significant also that spontaneous cures of psychopathy usually occur after the forties when instinct stress begins to diminish.

Regarding developmental predisposition, it may be said that the first five years of mental development are as important in psychopathy as in every other form of mental disorder. Nevertheless we have not yet reached the stage when different types of psychopathy can be correlated with different types of emotional experience in childhood, as can be done to some extent in the case of the neuroses and psychoses. The difficulty is to establish the nature of the endopsychic factors which, interacting with environmental stresses, produce the specific predisposition to psychopathy. In other words,

the environmental factor in early childhood is not simply a precipitating factor acting on a constitutional factor; it interacts with primary unconscious mental processes. In later life the environmental factor is purely precipitating; although it is to be noted that the psychopath, like the psychotic, reacts to minor frustrations as if they were major traumata.

A number of subdivisions of psychopathy are possible; socially regarded they can be divided into criminal and non-criminal; criminal types can be divided further according to the type of offence, in particular whether it takes a violent form. Swindling psychopaths are rarely violent. Aggressive psychopaths can be further subdivided into sexual and destructive types. Singling out the unconscious components involved, special attention must be paid to the exhibitionistic type, particularly the impersonators. Psychopaths can also be classified according to the nature of ego-disorder, e.g. faults in reality proving or faults in unconscious conscience-formation. The latter can be traced to disorders in the processes of introjection and identification. There is no objection to using a number of classifying systems. Our researches are still in their infancy.

As regards prognosis, the outlook of cases taken early enough is by no means so unfavourable as is generally supposed. The principles of treatment depend on recognizing the various factors responsible for the condition. Clearly the problem of psychic stress has to be dealt with. Stressful environmental circumstances should be alleviated and special steps taken to provide and maintain a relatively unstressful environment. The predisposition factor should be dealt with by the usual psycho-therapeutic procedures: either analytical therapy (though owing to negative transferences that cannot be easily applied) or some of the various forms of rapport-therapy. Treatment calls for an almost saint-like degree of patience with the attempts of the psychopath to find the weak points in the therapeutist's armour, particularly his reactions to disappointment and frustration. Therapy needs to be reinforced by the helpful attention of a number of supporting persons and agencies. The psychopath requires to exist for lengthy periods in a specially doctored environment.

[*March* 9, 1954]

DISCUSSION ON THEORY AND PRACTICE IN ANALYTICAL PSYCHOLOGY

[*Abridged*]

Dr. E. A. Bennet:

The Collective Unconscious

A statement by Jung—"the basic structure of the human psyche is as little personalistic as the body" (1939)—may serve as a prelude to the discussion of a distinctive concept in analytical psychology—the hypothesis of the collective unconscious. The term *collective unconscious*, often misunderstood, means that within the psyche there exists impersonal material, found in all men as part of their psychic structure. *Objective psyche* and *autonomous psyche*, which give a positive connotation, are used by Jung as alternatives to *collective unconscious*, and they have much to commend them.

Jung is right when he says, "None of my empirical concepts has met with so much misunderstanding as the concept of the collective unconscious psyche, a functional system, consisting of pre-existent forms, of a universal, collective and non-personal character, which does not develop individually, but is inherited." (1936).

The first glimpse of this non-personal, objective psyche came to Jung in the year 1909. In this year Freud and Jung made a trip to the United States to give a series of lectures and they seized the opportunity afforded by daily contact to engage in mutual analysis. During these analytical sessions Jung reported a dream to Freud in which, briefly, he found himself in an ancient house with two cellars and beneath the second were skulls and prehistoric remains. Freud's interpretation was not convincing to Jung and seemed not to do justice to the dream. Jung, in later reflections upon this dream, which contained elements beyond the range of personal associations, came to see in it a picture of the developmental stages of the human mind; the house, the cellars, the prehistoric remains being the cultural periods through which mankind had passed—the germ of the collective unconscious.

Whilst Freud never accepted Jung's developed work on the collective unconscious, there are indications—they have been termed "his incursion into the region of phylogenetic speculation" (Glover, 1950)—that Freud was aware of non-personal psychic elements. He writes: "memory very often reproduces in dreams impressions from the dreamer's early childhood . . . Beyond this, dreams bring to light material which could not originate either from the dreamer's adult life or from his forgotten childhood. We are obliged to regard it as part of the *archaic inheritance* which the child brings with him into the world, before any experience of his own, as a result of the experience of his ancestors" (Freud, 1949).

Dr. Ernest Jones (1953), however, claims that this material arises from the dreamer's childhood: "Now in the psycho-analysis of individuals we have in a number of cases been able to demonstrate

that ideas closely parallel to totemistic belief had been cherished during infancy, partly consciously, partly unconsciously.... In other words, we have before us in the individual the whole evolution of beliefs, and customs or rituals based on them, which is parallel to what in the field of folklore has run a course of perhaps thousands of years."

Freud merely noted the existence of non-personal psychic elements and offered no evidence to support a belief in them, possibly because they played no part in his therapeutic system. Dr. Jones, on the other hand, advances what appears to be the familiar recapitulation theory. Proof or exposition of this theory would seem to be required, for apparently it plays an essential part in the therapy.

Jung saw the need to give evidence in favour of his theory of the collective unconscious. "The hypothesis of the collective unconscious", he writes, "is just about as daring as the assumption that there are instincts... and the instincts are by no means merely personal peculiarities. The instincts form very close analogues to the archetypes—so close in fact that there is reason for assuming that the archetypes are the unconscious images of the instincts themselves." "Since archetypes are psychic products," he continues, "one possible source of proof lies in *dreams* which have the advantages of being involuntary spontaneous products of the unconscious psyche. Naturally we should, by investigation, exclude all motives in the dreams which were, or might be, known to the dreamer, and look for those which could not be known to the dreamer and yet behave functionally in his dream in such a manner as to coincide with the functioning of the archetype known from historical sources" (Jung, 1936).

Other sources of proof would be the waking dream of the schizophrenic, fantasies in trance states and the dreams of early childhood. Such material is often paralleled in mythological forms, and Jung studied mythology and alchemy in an effort to understand the obscure, impersonal content of dreams. The term *amplification* is used to describe this process of comparison. A similar procedure —the *comparative method*—is used in anthropology, and in philology the corresponding term is *collation*.

Amplification constantly provides an understanding of the obscurities in a dream or schizophrenic statement. Patients in analysis may use amplification in working alone upon their dreams, for they must bear their part in the treatment. Doctor and patient by the use of this procedure find much to support the validity of the concept of the collective unconscious and, consequently, of archetypes. Thus theory is confirmed by clinical experience.

The question Jung asked was a simple one: were there or were there not these pre-existent archetypal forms? He found evidence—too detailed for inclusion here—which supported the view that there were, and he believes that if others had observed the phenomena he describes, they would have reached the conclusions he reached. Yet he did not claim that the hypothesis of the collective unconscious or objective psyche is the only possible one. But to him—and to others—the theory explains the facts better than any other yet advanced.

An intellectual appreciation of this theory takes us only part of the way. Toynbee (1949) puts the matter vividly: "However far into the boundless realm of the Unconscious we may succeed in carrying the victorious invasion of the intellect, I fancy we shall always reach a point at last, at which the only practical policy proves to be Plato's policy of taking the Unconscious on its own terms... allowing the Unconscious to speak for itself."

Spontaneous painting and modelling occupy an important place in the practice of Analytical Psychology, the purpose being to form a bridge between the subject and the object, for clearly there can be no experience of an object—and so none of an objective psyche—without a subject. This mode of expression provides an example of *active imagination*. By *imagination* is meant the power which the mind has of forming concepts beyond those derived from external things presented to the senses, that is, the creative faculty. The creative process is not passive and the images depicted in painting, &c., express an activity—hence the name *active* imagination.

The systematic use of this method—difficult and even dangerous—requires considerable experience and judgment. As a rule it is employed in the later stages of analysis. It possesses one great advantage, namely, we get the unconscious material in a conscious state, rather than through the medium of the dream which may be fragmentary and uncertain.

Jung developed *active imagination* from Freud's technique of free-association; but in its present form active imagination and free-association have little in common. Active imagination is in no sense a "golden rule" in analysis and often it is not used at all.

Active imagination often reveals, in a convincing manner, some psychological happening—that is, some effect—which eludes precise description. The reality of the experience is not in question, but it cannot be set out in so many words. That which carries over the effect, the energy, of the unconscious we describe as a symbol. In Jungian psychology the symbol is the attempted expression of something unknown, for certain collective notions can only be expressed symbolically. For example, in *The Times* (1954) there was a correspondence upon the symbolism of the mace. Was it the symbol of the Speaker's authority or the symbol of the authority of the House? The correct answer, we learnt was that the mace symbolizes the royal authority—which is why Members of Parliament bow to the

mace as well as to the Speaker. Were it possible to define the royal authority, in so many words, a symbol would not be required.

"The symbol does not define nor explain, but points beyond itself to a meaning darkly defined . . . and not to be adequately expressed in any words of our current speech," so writes Jung, and further, "The symbol being the possibility and intimation of a meaning higher and wider than our powers of comprehension can seize." Thus "the energy is led over into a new object; for the symbol is the psychological machine that transforms energy" (Jung, 1928) and, consequently, makes it available. This availability of energy through the symbol is seen in all religious systems and in many political movements and crusades—indeed in all human activities when the petty personal life is enlarged and transformed and the personality finds a new centre.

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Dr. F. O'Donnell Finigan:

Analysis

Analysis is a joint endeavour whereby a human situation and a technique become complementary to a mentally creative process. A patient comes to analysis because of an overwhelming need to face with someone else what he cannot face alone, namely his unconscious. This is the essence of analysis, and it requires the united and sustained effort of both analyst and patient.

The principal instrument of therapeutic procedure in analytical psychology is *dream analysis.* Dreams are autonomous spontaneous expressions of the human psyche, expressing both the conscious and unconscious attitudes of the individual. They are the fundamental source of knowledge as to what is happening in the unconscious. The psyche of the baby is the relatively undifferentiated matrix from which emerge *consciousness, self-awareness, the ego,* and ultimately *the self.* It appears probable that in sleep we return to make contact with this psychic heritage. Dreams are the most reliable intimation of what is occurring in the unconscious when this contact takes place.

During the initial interview, frequently before the history has been completed or a diagnosis is reached, a previous dream may be mentioned by the patient, which is often significant and may be a simple and clear constellation of his problems and his unconscious attitude to seeking psychological help. Frequently it possesses a creative and synthesizing quality suggesting the manner in which his problems might be solved. A dream series can be more readily understood than an isolated dream, and later dreams may indicate the need for amplification or re-interpretation of earlier dreams. To the patient is commended the value of writing down each dream on waking, the ideas he associates with it, the current circumstances of his life, and the place and date of the dream.

In analysis, *procedure is flexible;* no programme is formulated; psychic material is analysed as it offers itself. Only general principles and working rules are applicable. The analysis is along the lines of an ordinary conversation, both patient and analyst being seated comfortably; a couch is rarely used. The more informal and spontaneous the analyst, the more at ease and natural is the patient, and under these conditions problems are likely to be seen in their true perspective.

At an early stage, it is important to establish a personal human contact with a patient. The adult nature of this relationship is stressed, and the importance of meeting each patient in his own right as an individual is regarded as fundamental. Gradually he comes to feel that he is valued for himself, and that the extent of his difficulties and the degree of his achievements are recognized.

Before reaching a provisional opinion as to the patient's suitability for analysis, the anamnesis is completed, and a provisional diagnosis made, bearing always in mind the possibility of the presence of relevant organic factors. When analysis is indicated, the implications are explained in detail to the patient, who is encouraged to express doubts and misgivings, to ask questions and arrive at his own assessment. Should there be mutual agreement, then analysis proceeds as a continuance of preceding interviews and with the same flexibility. A series of interviews takes place, each of fifty minutes' duration, two or three times a week, the time between interviews is necessary for the digestion and assimilation of what has happened.

Amplification.—Amplification in analytical psychology is the method of dream analysis. Each item, together with the personal associations for the dreamer, is considered in detail. Then further

associations of a more general character are expressed, for example, association with a familiar mythological theme. These are usually expressed in part by the patient and in part by the analyst, and in this way gradually each item is amplified, and by a similar process each is linked up, so that finally the dream is seen as a whole, with imagery enriched, extended and amplified, and now coloured by the revealed emotional content which may spring from the repressed emotion of infantile experiences or from the emotion of experiencing for the first time collective or archetypal images.

The dream is now seen not only as an expression of infantile conflicts and desires, but also as part of the broad background common to all humanity as expressed in myths, folklore, fairy tales, &c., emphasizing the recurring theme of this common background. *Thus a sequence of dreams assumes gradually the form of a new myth specific to the dreamer.* The analyst seeks in every way to encourage the patient to become conscious of this unfolding myth and so to become increasingly aware of his own problems and how best to meet them, to recognize his own potentialities, thus gaining a sense of direction in his life, and even possibly some intimation of his place in the scheme of things.

Active Imagination.—This is the process by which unconscious activity can be perceived and experienced during the waking state. It can be used for further elaboration of a dream, to canalize unconscious expression between interviews, to overcome resistance, or to express some aspect of the unconscious for which the spoken word is inadequate. An essential part of the discipline of active imagination is committing it to some form such as writing, doodling, drawing, painting, modelling, musical composition, &c., to which patient and analyst can if need be later return, and it acts as a safeguard against mere unproductive day-dreaming.

Transference.—Transference in analysis is a special example of projection, and consists of a process in which the patient identifies the analyst with aspects of his own unconscious images, feelings and ideas, and he reacts emotionally as if these projections or identifications were objectively present in the analyst. These emotions may be positive or negative, and when positive, the analysis proceeds smoothly, whereas when the reverse is the case, the analysis is stormy and the analyst can be certain that he is meeting important and as yet unacknowledged problems and at times resistance.

The adult relationship between patient and analyst, and the ordinariness of procedure during an analytical interview, enable the patient to test his projections repeatedly against the reality of the analyst and the analytical relationship. This has the effect of confining transference to an extent appropriate for each patient, and experience shows how widely variable in extent and importance this is. Accordingly, the analysis but rarely becomes "transference analysis". It is probable that the more impersonal and enigmatical and the more hidden from view is the analyst, the more readily will the patient project his unconscious images and feelings on to him.

Transference is usual though by no means invariable. It needs to be recognized at once, but should only be interpreted when necessary. The art of interpretation lies in recognizing what is appropriate, saying neither too much nor too little, but at the right time.

Counter-transference, like transference, is an unconscious process in which the analyst may project his unconscious images on to the patient, and he is thus affected in spite of himself. The analyst needs constantly to be aware of this process whenever it is occurring; otherwise, the analysis may founder. On occasions, some interpretation to the patient is necessary.

Resolution of the transference and counter-transference.—In most analyses, resolution occurs *pari passu* with other aspects of growing consciousness. The process of resolution becomes complete towards the end of analysis—provided that the analyst is willing during this latter phase, when analysis merges into a more objective dialectical discourse, to reveal himself, if it is appropriate, as he really is.

When an analysis is completed, the capacity to become more conscious, learned through the experience of analysis, continues in everyday living, and so maturation proceeds towards psychic completeness. Jung describes this as the process of individuation, leading ultimately to the realisation of the Self. But what of the patient in whom it does not occur, for this is neither automatic nor invariable? The analyst needs to remind himself that resolution is by no means certain, and expectant treatment along supportive lines is sometimes indicated, for who can know what is incubating in the depths of the unconscious?

Dr. Anthony Storr:

Cybernetics and the Psyche

This paper is confined to one aspect of analytical psychology: Jung's concept of the compensatory function of the unconscious. In discussing Jung's work it is important to remember that he does not claim absolute validity for his ideas: he regards all psychological theories as being largely subjective—points of view, not creeds which must be believed.

One of his ideas which receives scant attention is that the psyche is a self-regulating system, an

idea which should appeal not only to psychiatrists, but also to physiologists and physicians, and to those who are interested in cybernetics. The body contains a large number of homeostatic mechanisms which serve to regulate the internal environment in such a way that the optimum conditions for the life of the individual may be maintained; this is brought about by a system of negative feed-backs, which, when a change in the internal environment occurs in one direction, tend to encourage a change in the opposite direction. Wiener, in his book on Cybernetics (1948, New York), gives as examples the regulation of calcium metabolism, of the heart-rate and blood pressure, of the hydrogen-ion concentration of the blood, and other examples. The life of the body is thus conceived as proceeding along a middle course between pairs of opposites: neither too hot nor too cold; neither osteoporotic nor calcified; neither hypertensive nor hypotensive. A self-regulating system in fact, in which excesses in any direction are barred; or if not barred, at least dearly paid for in illness, discomfort, or death.

Jung's conception of the psyche is very similar. He maintains that there is a reciprocal relationship between the conscious and unconscious parts of the psyche; and that when this relationship is disturbed, as is the case in a neurosis, there will be an attempt on the part of the psyche itself to remedy this state of affairs. If the conscious attitude is disturbed, the unconscious will attempt to correct the distortion. It follows from this that a neurosis may be regarded not only as an unpleasant disturbance to be got rid of, but also as an attempt at self-cure. Moreover, an extreme attitude in consciousness will evolve an extreme reaction in the unconscious, so that there will be a tendency for the conscious attitude to be reversed.

Extremes tend to evoke extremes: and one can safely assume that the fanatic is the prey of unconscious doubt; that the man who parades his strength is secretly uncertain of himself; and that the day-dreamer conceals within him a man of action.

In neurosis, the balance of the opposing forces is disturbed; and treatment is directed towards restoring the equilibrium. The contents and tendencies therefore of both the conscious and unconscious parts of the psyche have to be considered so that the two can be integrated rather than dissociated. Conscious attitudes and tendencies can be assessed by the ordinary method of taking a history of the individual's development. The investigation of the unconscious is undertaken by dream analysis.

Dreams are regarded by Jung as a natural phenomenon. He does not accept the point of view that all dreams are a distorted expression of unconscious wishes, for he feels that a manifestation of psychic activity which is so rich and varied as the dream cannot be reduced to a simple formula. One important aspect of the dream, however, seems to be that it has a compensatory function in relation to consciousness. As an example, I will quote a dream told me by a girl of 26 who had had this dream on several occasions in childhood.

"My mother has sent me to the bottom of the garden. As I go, a steam-roller chases me and I run on terrified. I reach the end of the garden where there is a fence which I cannot get over. As I reach it my mother appears on the other side of the fence and laughs at me."

In this dream it is clear that the mother appears in a most hostile guise. She is the initiator of a situation in which the patient is in danger of being crushed, and jeers at her. From the patient's history it was discovered that she had had a severe disability in childhood, which had resulted in her being over-protected and coddled by her mother. The dream pointed out this danger of her being overwhelmed by maternal solicitude long before there was any evidence of overt neurotic symptoms, which only occurred much later in life, at the time of her marriage. The dream is clearly the unconscious reaction to the dreamer's overdependence on the mother: an illustration of the compensatory function of the unconscious.

Jung thinks that in trying to understand unconscious material we ought to take into account not only what gives rise to the material—the causal aspect, but also the direction in which it seems to be pointing—the teleological or final aspect. In cybernetics machines which possess feed-back exhibit "goal-seeking" properties; the "behaviour" of the machine can only be understood fully in terms of the state towards which it is changing. In the body, for instance, the mechanisms which operate in response to a change of temperature are best understood in terms of the "goal" towards which the various changes in the body are directed, which is the maintenance of the normal temperature. In the example given, the goal towards which the dream pointed was the achievement of freedom from the undue influence of the mother.

Jung regards the psyche as goal-seeking in the same way as the exponents of cybernetics regard the body as goal-seeking. In the case of the body, the ultimate goal might be thought of as homeostasis: in the case of the psyche, the achievement of an integration between conscious and unconscious. One set of forces opposes and balances another set of forces in the psyche: and the individual's ability to lead a creative and satisfying life depends on the balance of power being reasonably equable: just as co-ordinated movement is only possible when agonist and antagonist work smoothly together, although their actions oppose one another. The ultimate goal is the living expression of whatever capabilities are inherent in each individual; and the attainment of this goal depends upon the opposing factors in the psyche being reconciled in a harmonious whole so that they can co-operate in opposition like agonist and antagonist. Jung calls this reconciliation the Self.

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Section of Odontology

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Some Recent Advances in the Study of Carbohydrate Degradation in the Mouth

By R. L. HARTLES, B.Sc., Ph.D.

Senior Lecturer in Dental Biochemistry, School of Dental Surgery, University of Liverpool

SUMMARY.—The metabolism of carbohydrates in the oral environment is discussed.

Manometric methods are very suitable for the study of carbohydrate breakdown in the mouth, only small amounts of material being required. Results of the overall metabolic products can be obtained as also a knowledge of particular enzymic processes.

The use of enzyme inhibitors to reduce acid production in the mouth is discussed briefly.

The study of the breakdown of carbohydrates in the oral environment is concerned in the main with problems of chemical microbiology and enzymology. The ultimate object is to explain in biochemical terms the complex life of the many micro-organisms living in mixed association in the mouth. It is the way in which the whole flora behaves which is important from the dental point of view, and results obtained by various methods of attack must be related finally to the natural oral environment.

The several methods of approach to research in chemical microbiology were lucidly stated by the late Marjory Stephenson, and Woods (1953) has admirably summarized her views. In these methods as they relate to the study of mixed human saliva the term "saliva" includes its contained cellular material unless otherwise stated. There are some five levels at which investigations can be carried out. First, we can study the whole saliva and dental plaque material; these are mixed cultures in their natural environment. Secondly, pure cultures of oral micro-organisms can be studied in complex undefined media. Thirdly, mixed cultures or pure cultures can be studied in chemically defined media. Fourthly, we can investigate washed suspensions of organisms in the presence of defined substrates. Finally, we may study cell preparations with defined substrates to gain knowledge of the enzyme systems involved. All these methods are equally valuable, the emphasis may move from one to the other, but eventually all the knowledge gained must be related to the natural environment. It is desirable, therefore, that the problem of carbohydrate metabolism in the mouth should be studied at as many levels as possible.

It is the intention of this short review to consider briefly an approach to the study of whole saliva·

General metabolic picture in saliva.—From the dental point of view the aspect of oral biochemistry which has received most attention is the ability of the saliva and the dental plaque to convert certain carbohydrates into acids in sufficient quantity to cause dissolution of the tooth minerals. Whether this dissolution actually occurs or not depends, of course, on many other factors such as the removal of the acid formed and the resistance of the teeth to demineralization.

Various reports have been made concerning the production of acid and caries activity. Fosdick *et al.* (1937) devised a test for caries susceptibility by incubating saliva with glucose and calcium phosphate at 37° C. and measuring the amount of calcium dissolved by the acid formed. Snyder (1940) used an acid/base indicator to determine the acid produced when saliva was incubated with glucose. Stephan (1944) considered that after a glucose rinse there was a greater drop in pH on the tooth surfaces of subjects with active caries than on those who were caries-free; but there was a considerable drop in pH even in the latter. In none of these tests is there complete parallel between acid production and caries activity in every case.

Many *in vitro* methods of studying acid production require incubation of saliva/carbohydrate mixtures for a considerable time, in some cases for days. It is obviously desirable to be able to study carbohydrate breakdown over short periods, especially in the first minutes after carbohydrate comes in contact with the saliva. For this purpose manometric methods are eminently suitable, only small amounts (0·5–1 ml.) of saliva are needed, the "basal" or "endogenous" metabolism of the resting fasting saliva can be studied and the effect of the addition of a variety of carbohydrate substrates can readily be determined. Two lines of attack are possible: the study of oxygen consumption and of acid production. Various workers have used this approach (Hartles and McDonald, 1950; Neuwirth and Summerson, 1951; Calandra and Adams, 1951; Pearlman, 1951; Burnett, 1952; Hartles and McLean, 1952; Hyden and Hein, 1953; Hartles and Wasdell, 1954*a* and *b*).

Oxygen consumption of saliva.—Using manometric methods, Hartles and McDonald (1950) showed that resting whole saliva consumes oxygen. When glucose was added the oxygen consumption was approximately doubled. Burnett (1952) reported that respiration in salivas with a high endogenous oxygen consumption increased less on the addition of glucose than those with a low consumption. When the lactic acid production in saliva was measured under these aerobic conditions it was found that no detectable lactic acid was produced in the absence of added glucose, but appreciable quantities were produced by all subjects when glucose was added. Neuwirth and Summerson (1951) reported similar results and confirmed that there was no apparent relationship either direct or inverse between oxygen consumption and lactic acid production. These latter workers showed that the addition of lactic acid to saliva caused an increased oxygen consumption, in other words, saliva could oxidize lactic acid.

Effect of anaerobic conditions.—In an atmosphere of N_2 containing 5% CO_2 the resting saliva again produced no detectable lactic acid until glucose was added, when twice as much lactic acid was formed as in the presence of oxygen (Hartles and McDonald, 1950). Neuwirth and Summerson (1951) confirmed the observation of the above workers that lactic acid was only a portion ($\frac{1}{8}$ to $\frac{1}{3}$) of the total acid produced.

Filtered saliva.—Several workers have reported that saliva which has been passed through a Seitz filter, or has been subjected to centrifugation, neither consumes oxygen nor produces acid. It can, therefore, be concluded that the presence of cellular material is necessary for both oxidative and fermentation processes (Sreebny *et al.*, 1950; Hartles and McDonald, 1950; Tullar, 1953).

These results give an overall general picture of the salivary metabolism. We know that both aerobic and anaerobic processes can take place in the appropriate circumstances. It is attractive to consider the possibility of an inverse relationship between oxygen consumption and acid production. Generally speaking, anaerobic reactions produce more acidic products than do aerobic processes. Burnett (1952) claimed that in several subjects high salivary respiration was associated with freedom from caries, but this report has not yet been confirmed by other workers. The addition of cyanide to saliva (to prevent the utilization of oxygen) causes a great increase in lactic acid production in the presence of glucose (McDonald, 1951). It is not unreasonable to postulate that anaerobic conditions may exist in certain areas in the mouth, for example under a dental plaque or at the base of a deep fissure. Such conditions would favour the production of acid. Calandra and Adams (1951) confirmed the observation of Neuwirth and Summerson (1951) that saliva readily oxidized lactic acid in the presence of oxygen. They also showed that other products of carbohydrate breakdown such as pyruvate, acetate and propionate were less readily oxidized.

It appears to be established that all salivas produce acid to a greater or lesser degree and the almost inescapable conclusion is that acid production *per se* is not the only factor in dental caries. In fact, one subject who was clinically and radiographically caries-free produced aerobically far more lactic acid than any of a group of caries-active subjects. One very interesting observation on this caries-free subject was that in anaerobic conditions his lactic acid production was less than in the presence of oxygen (Hartles and McDonald, 1950). This was unusual and it may be that in

certain circumstances lactic acid is formed by an aerobic process, suggesting a departure from the Embden-Meyerhof scheme of glycolysis.

One of the reasons for so many conflicting reports concerning salivary metabolism is that we lack fundamental data concerning the mode of carbohydrate breakdown in the mouth. Until we have some information concerning the enzymic composition of the whole saliva little interpretation of results will be possible. This is obviously a task which will take many workers a great deal of time. In a very small way workers in the author's laboratory have begun to investigate saliva from this point of view. It seemed logical to begin at the beginning and investigate the ability of saliva to split and metabolize a variety of oligosaccharides.

The carbohydrases of the whole saliva.—The only carbohydrase which has unequivocally been shown to be a component of the glandular secretions is α-amylase. This enzyme, which has been isolated and crystallized by Meyer *et al.* (1948), hydrolyses starch to maltose and maltotriose; no glucose is formed by the action of salivary α-amylase on starch (Roberts and Whelan, 1951). Hartles and Wasdell (1954*a*) studied the utilization of four different sugars by saliva and found that, in 10 subjects studied over a long period, fructose was oxidized less readily than glucose, maltose or sucrose. The disaccharides maltose and sucrose were metabolized as readily as glucose. There must therefore be enzymes present which can split these disaccharides to their component monosaccharides so that they may be further oxidized. It is of interest to know whether these enzymes are produced by the oral flora or by the salivary glands.

Hartles *et al.* (1954) have studied an oral strain of lactobacillus which, in washed suspension, did not metabolize maltose or sucrose. When a sample of commercial invertase was added to the suspension, glycolysis occurred readily in the presence of sucrose. This fortunate occurrence enabled them to use the organism as a tool in investigating the location of invertase (sucrase) and maltase activity in the saliva. If the addition of any salivary fraction to their lactobacillus resulted in glycolysis in the presence of maltose or sucrose, then that fraction must have contained an enzyme capable of splitting maltose or sucrose. They have used centrifugation and filtration to obtain various saliva fractions as well as collecting parotid gland secretions. By these methods it was shown that such enzymes were confined to the inside of the cells, they were present neither in the secretion of the paratid gland nor extracellularly in the whole saliva. This means that before being split into fractions, which can be metabolized to acid, maltose and sucrose must enter the cells of the micro-organisms. This point is worthy of emphasis.

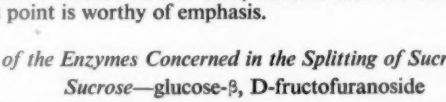
The Nature of the Enzymes Concerned in the Splitting of Sucrose and Maltose

Sucrose—glucose-β, D-fructofuranoside

There are two well-known enzymes which can hydrolyse sucrose. Kuhn (1923) was perhaps the first to realize this fact. One is termed α-D-glucosidase (glucosaccharase or glucoinvertase) which attacks a saccharide having a free terminal glucose molecule; the other, a β-fructofuranosidase, attacks a saccharide having a free terminal fructose molecule. The molecule of sucrose exhibits both these requirements and can therefore be split by both enzymes. Which one, then, is present in saliva? Or are both enzymes present?

Recently attempts have been made to solve this problem by using trisaccharides of known composition which are substrates for specific enzymes (Hartles and Wasdell, 1954*b*).

Raffinose, galactosyl-glucosyl-fructose has a terminal fructose but no terminal glucose. It is, therefore, a substrate for β-fructofuranosidase but not for α-glucosidase.



Raffinose

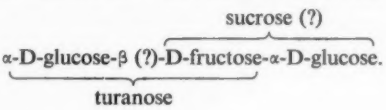
Raffinose was metabolized by whole saliva. There are two possible mechanisms: first, the linkage between glucose and fructose may be hydrolysed, thereby releasing fructose which can then be further attacked; secondly, the linkage between galactose and glucose may be split, releasing galactose and sucrose. This second mechanism, however, can be discounted, for it was shown that melibiose was not metabolized by saliva. Therefore there is strong presumptive evidence for the conclusion that sucrose and raffinose are hydrolysed by a β-fructofuranosidase.

There still remains the possibility that α-glucosidase (glucosaccharase, glucoinvertase) also contributes to the hydrolysis of sucrose.

Weidenhagen (1930) has put forward the theory that all α-glucosidic linkages are split by the same kind of enzyme α-D-glucosidase. He bases his view on his observations that purified yeast maltase

hydrolyses maltose, sucrose and melezitose (which are all α-glucosides). Maltase preparations obtained from other sources, however, do not split sucrose (Tauber and Kleiner, 1933, 1934; Hofmann, 1934). The specificity of maltose is well reviewed by Gottschalk (1950). Most of the work appears to have been done on the yeast enzyme and on a maltase obtained from *Aspergillus oryzæ* (taka-maltase). It is considered that the latter enzyme is a little more specific, but Gottschalk (1950) believes the differences to be very small.

Experiments with melezitose and turanose.—The trisaccharide melezitose is not metabolized by saliva, whereas the disaccharide turanose is. The relationship between the two sugars is as follows:

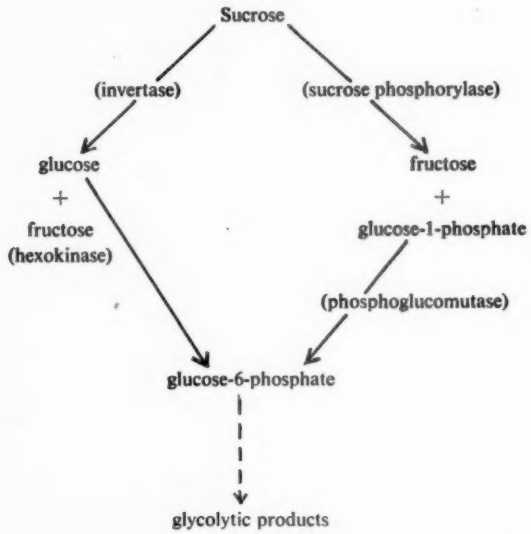


Melezitose

The enzyme glucosaccharase (glucoinvertase) converts melezitose into glucose and turanose (Hudson, 1946; Isbell, 1941). If this enzyme is present in saliva the trisaccharide should be metabolized since the products are known to be readily attacked by saliva. This does not happen, and we consider that although the evidence is negative it strongly suggests that glucoinvertase is absent from saliva, and that the only sucrose hydrolysing enzyme present is a β-fructofuranosidase. It is interesting to note that turanose is readily metabolized by saliva. Since melezitose is not split this supports the view of Bridel *et al.* (1927) that there is a specific turanase which they found in bottom yeast distinct from the α-glucosidase which attacks melezitose.

From the above work it can be concluded that the maltase present in saliva will not hydrolyse melezitose.

There is a further possible pathway for sucrose breakdown. Doudoroff *et al.* (1943) have demonstrated that *Pseudomonas saccharophila* contains an enzyme sucrose phosphorylase. This converts sucrose into glucose-1-phosphate and fructose.



If a specific inhibitor for hexokinase could be found, it might be possible to decide whether this system operated in saliva. So far, work in the author's laboratory, using amidone as a hexokinase inhibitor, has produced no clear-cut evidence, but the point is worthy of further investigation.

Other carbohydrases in saliva.—Chauncey and Lisanti (1953) have reported that whole saliva contains amongst other enzymes β-glucuronidase, β-D-galactosidase, hyaluronidase and sulphatase. Knox (1953) has shown that several oral micro-organisms have a mucolytic activity (split mucin).

Little is known of the function of these enzymes, but one cannot overlook the possibility of hyaluronidase and mucinases being concerned with the existence of the dental plaque.

The rapidity of acid production in the mouth.—Evidence has been obtained to show that the process of acid production, following the introduction of fermentable carbohydrate into the mouth, is very rapid indeed. Stephan (1944) showed after a glucose rinse the pH of the dental plaque fell to a minimum in 3–10 minutes. Neuwirth and Klosterman (1940) allowed a glucose pellet to dissolve slowly in the mouth and determined the lactic acid produced. They found that the lactic acid concentration in the saliva reached a maximum in 10–15 minutes. After a glucose rinse the maximum lactate concentration in the saliva was reached in many cases within 5–10 minutes (Hartles and McLean, 1953). The latter workers also drew attention to the rate of removal of the formed lactate; salivary values returned to normal within 30 minutes of rinsing with 10% glucose solution.

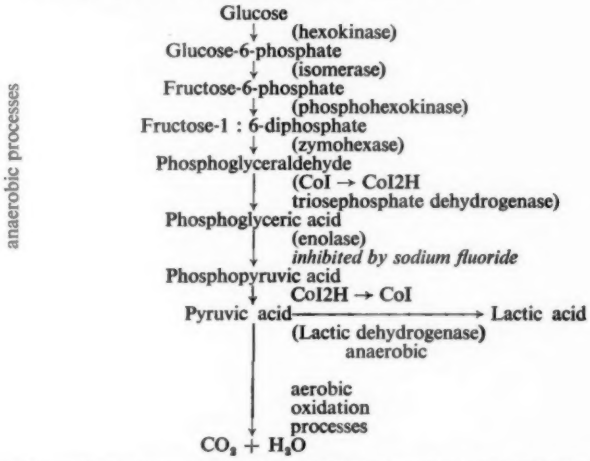
The Use of Enzyme Inhibitors to Reduce Acid Production in the Mouth

In 1936 Fosdick and Hansen suggested that the mechanism whereby acids are formed in the mouth from carbohydrates was the same as that occurring in the anaerobic breakdown of carbohydrate in muscle tissue. It has indeed been shown that many micro-organisms utilize carbohydrate anaerobically in much the same way as does the mammalian muscle.

In order to form acid in the mouth it is necessary to have a fermentable carbohydrate and the requisite enzyme system. Theoretically, therefore, it should be possible to inhibit one or more of the enzymes concerned in the acid production and so reduce the amount formed. There are, of course, many difficulties in achieving this object. The inhibitor must be non-toxic when absorbed into the blood stream. It must remain in susceptible areas of the mouth for a considerable time. It must not be unpleasant to use, and must not be destroyed by admixture with other things found in the mouth.

Fig. 1 shows the breakdown of glucose as it occurs according to the Embden-Meyerhof scheme of glycolysis.

THE GLYCOLYTIC ROUTE OF GLUCOSE BREAKDOWN



To be effective in reducing acid production from carbohydrate, inhibition must be in the early stages of glycolysis.

FIG. 1.

In muscle the lack of O_2 leads to the production of lactic acid. That is, pyruvic acid is reduced to lactic acid to enable CoI2H to be reoxidized to CoI so that energy can still be obtained anaerobically. If oxygen is supplied the pyruvate is converted to $CO_2 + H_2O$ and the amount of lactic acid produced falls. If saliva is allowed to metabolize glucose in the absence of oxygen much more acid is produced than in its presence (Hartles and McDonald, 1950). It is important to appreciate this fact when we consider possible inhibitors. For example, sodium cyanide completely stops the respiration (i.e. oxygen consumption) of saliva, but it encourages the production of acid (McDonald, 1951). This is because cyanide is known to inhibit the cytochrome oxidase system which is necessary for the utilization of oxygen. The system is therefore compelled to fall back on anaerobic processes which lead to the accumulation of acid metabolites. This kind of inhibition (even if it were not contra-

indicated for more obvious reasons) is of little value for our purposes. It is necessary to find something which inhibits the sequence before the production of acid.

Fluoride.—Sodium fluoride inhibits the enzyme enolase by forming a complex with the Mg^{++} ions which it requires as co-enzyme. This property may contribute to the effect of fluoride in reducing the incidence of dental caries. Recently, however, Wright and Jenkins (1954) have reported that the amounts of fluoride likely to be found in the saliva of subjects living in either "high" or "low" fluoride areas are insufficient to affect the production of acid by the oral flora.

The Effect of Ammonia and Urea on Acid Production in the Mouth

It has been claimed that ammonia and urea reduce the amount of acid produced by the oral flora from carbohydrates (Kesel *et al.*, 1946; Stephan, 1943), and that one factor is that basic ammonium salts such as dibasic ammonium phosphate inhibit the growth of lactobacilli. Jenkins and Wright (1950), studying this problem, found that there was no difference in the amount of ammonia produced by the salivas of caries-active and caries-free subjects. This result was confirmed by Ludwick and Fosdick (1950). More recently Wright and Jenkins (1953) have reported a positive correlation between ammonia concentration and acid production in saliva. Kesel *et al.* (1954) are of the opinion that ammonia and urea are factors in a natural mechanism which resists dental caries activity and can be used to assist it. Nevertheless, the only real objective observation available is that *in vivo* and *in vitro* ammonium salts and urea inhibit the growth of lactobacilli. This was confirmed by Pearlman and Hill (1951), who also showed that 4M urea completely inhibited glycolysis in *Lb. acidophilus*; this is, however, a tremendously high concentration of urea. The results available do not really justify the use of an ammoniated dentifrice for the control of dental caries. No evidence has been produced to show which stage in carbohydrate metabolism is inhibited by ammonia. It cannot, therefore, at this stage be classed as an "anti-enzyme".

The Effect of Chlorophyll on Acid Production in the Mouth

The only way in which an alleged caries-reducing agent can be tested is by an adequately controlled clinical trial. All other methods such as inhibition of acid production, lactobacillus counts, &c., are possible aids to the screening of compounds or to investigating the natural processes occurring in the mouth. No adequate clinical trials have yet been carried out using chlorophyll derivatives. Various workers have reported that certain chlorophyll compounds had a bacteriostatic effect *in vitro* against oral micro-organisms and that acid production in saliva carbohydrate mixtures was decreased (Shafer and Hein, 1950; Bibby and Nevin, 1951; McBride, 1952).

Shaw (1950) reported that sodium copper chlorophyllin failed to reduce caries in the albino and cotton rat. Hein and Shafer (1951), however, claimed that copper chlorophyllin decreased dental caries in the hamster. This is an interesting observation suggesting possible differences in the carious process in the two species.

Use of Sodium N-lauroyl Sarcosinate and Sodium Dehydroacetate as Enzyme Inhibitors in the Mouth

An interesting development has recently been reported by Fosdick *et al.* (1953). They argued that if an enzyme inhibitor was to prove effective it must remain in the mouth for a considerable period of time. One way of achieving this was to find a compound that (*a*) inhibited acid production and (*b*) was adsorbed by or combined with the dental plaque material. After testing 381 compounds sodium N-lauroyl sarcosinate and sodium dehydroacetate seemed promising. They inhibited acid production and the inhibition persisted for some time after application of the inhibitor. Clinical trials have been reported showing that the use of a toothpaste containing sodium N-lauroyl sarcosinate reduces the incidence of dental caries (Fosdick, 1953). This approach, via an inhibitor which is adsorbed or reacts with the protein of the dental plaque, is a sound one; it is an important contribution to the finding of an inhibitor which persists in the mouth.

Little is yet known of the way in which these compounds inhibit the metabolism of carbohydrate. Fosdick (1954), when pressed for information, suggested that hexokinase was inhibited, but adequate proof has yet to be provided.

Other inhibitors of acid production in saliva.—The approach to the problem of finding an inhibitor is at the moment necessarily empirical. Many chemical compounds will inhibit acid production, but they have toxic or other undesirable side reactions. It is therefore of little profit at the moment to discuss these compounds.

Penicillin.—No mention has been made of penicillin. It reduces acid production in the mouth considerably (Zander and Bibby, 1947), but the desirability of using an antibiotic for this purpose is to be questioned.

Conclusions

(1) Saliva carbohydrate mixtures produce acid.
(2) As yet little is known of the precise biochemical processes in salivary metabolism.
(3) We must gain as much information as possible so that methods of combating acid production may rest on methods other than empirical ones.

To understand the role of carbohydrate degradation in dental caries we should know the intimate structure of the teeth, the nature of the attacking forces, and how those forces are mobilized.

"Only a small part of scientific progress has resulted from a planned search for specific objectives. A much more important part has been made possible by the freedom of the scientist to follow his own curiosity in search of truth." Those are the words of Dr. Irving Langmuir, a Nobel prize winner in chemistry. Perhaps if we forgot about dental caries for a while and just became curious about teeth and their environment we might accumulate sufficient knowledge to answer many questions.

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Dr. G. Neil Jenkins: Dr. Hartles has explained how the lactic acid formed by saliva comes from pyruvic acid present in excess of that which can be oxidized. What does he think is the limiting factor to this oxidation in the plaque? Is it oxygen tension, the concentration of co-enzymes required by oxidizing enzymes, or of these enzymes themselves? Has he any suggestions for following up Fosdick's idea of preventing acid accumulation by encouraging this oxidation rather than by inhibiting acid formation?

Dr. Hartles concluded that, because Seitz filtrates of saliva had no action on sucrose or maltose, the enzymes attacking these sugars are intracellular. It has been stated, and we have confirmed, that some enzymes are adsorbed during Seitz filtration. Unless it has been found, by independent tests, that an enzyme can pass through a Seitz filter, it would seem premature to conclude that a salivary enzyme absent from Seitz filtrates is intracellular.

With regard to the action of fluoride on carbohydrate metabolism, in saliva, it must be doubted whether it acts exclusively on enolase. If this were its action, then in its presence, glycerophosphoric acid would accumulate in lieu of lactic acid. The observed fact is, however, that, at least with high concentrations, fluoride reduces total acid production by saliva. Does not Dr. Hartles think that this indicates inhibition at some earlier stage of the Embden-Meyerhof scheme? Another point arises about fluoride. Since the concentration of soluble fluoride in the mouth seems to be too low to affect bacteria, can he conceive of any way in which fluorosed enamel, that is, fluoride in a tightly bound and insoluble form, could exert an antibacterial or anti-enzymatic action?

On the ammonia question, while it is true that high concentrations of ammonium salts exhibit antibacterial action *in vitro*, Dr. Hartles had, perhaps, not made clear that there seemed to be no evidence of a specific effect of the ammonium ion. We found that sodium salts were only slightly less active than were the corresponding ammonium salts, a fact which might not be apparent unless the actions of wide ranges of concentrations of the two salts were compared. We did not accept the view that the ammonium ion or urea exerted any antibacterial effects at physiological concentrations.

Finally, we have some preliminary results which indicate that starch may be broken down by a phosphorylase, which is an interesting parallel to the results of Dr. Hartles on sucrose. The presence of the anti-amylase known to be in wheat would prevent acid production from wheat flour or bread if the breakdown of starch depended on amylase action. We have found that acid is produced almost as rapidly from flour as it is from pure starch or even glucose, and conclude tentatively that saliva must contain some other enzyme, presumably a phosphorylase, which attacks starch. The presence of the anti-amylase in wheat probably means that salivary amylase is virtually without action on the main source of starch in Western diets. The possible danger to digestive enzymes of introducing non-specific enzyme inhibitors in dentifrices is probably unimportant as far as salivary amylase is concerned, since this enzyme is already inhibited when wheat products are eaten.

Dr. Hartles in reply: Dr. Jenkins has drawn attention to our lack of knowledge in several important instances. I do not know the limiting factor to oxidation in the plaque but we are trying to find out; it is almost certain to be one of those mentioned by him. We have given thought to the possibility of encouraging aerobic processes but so far with little success. I still think it is a good idea.

Concerning Seitz filtration, we did satisfy ourselves that invertase was not appreciably adsorbed by the filtration process.

The whole question of the inhibitory action of fluoride in the mouth requires further investigation. I agree with Dr. Jenkins that inhibition of enolase alone seems unlikely to account for the effects of fluoride.

Section of Dermatology

President—REGINALD T. BRAIN, M.D., F.R.C.P.

[*February* 18, 1954]

Case for Diagnosis—Nodular Moniliasis of Tongue.—ROBERT BOWERS, M.D., M.R.C.P., and IAN W. WHIMSTER, M.B.

Mr. G. H., aged 57, aircraft fitter.

History.—This patient was first seen by Mr. R. Harvey in February 1953, when he complained that a lump had been present on his tongue for about three months.

On examination.—Several firm raised lesions were observed arranged along each side of the median furrow of the tongue.

A biopsy was taken, and reported to show acanthosis and inflammatory infiltration of the submucosa. W.R. and Kahn negative.

I (R. B.) first saw him five months later when the condition appeared to have changed little. The lesions (Fig. 1) were painless, firm and raised; those nearest the back of the tongue were smooth and

FIG. 1.

red in contrast to those at the front which retained their papillæ and a fairly thick coat of fur. W.R. and Kahn were again negative; nothing abnormal was found on general examination except a blood pressure of 190/105 and some retinal arteriosclerosis. White cell count normal. In spite of a reduction in his cigarette consumption from thirty to one daily, the lesions remained unaltered; the sections were then referred to Dr. Ian Whimster.

Attempts to find anything similar in the literature have not been very successful though Brocq's "glossite médiane losangique" might be the same condition.

POSTSCRIPT (8.5.54).—On March 2, 1954, one large nodule of the tongue was anointed with Anethaine, and then infiltrated with Planocaine. Its epidermis and dermis to a depth of two or three millimetres were shaved off in horizontal slices and sent to Dr. R. W. Riddell. This tissue was ground up thoroughly, and pure cultures of *Candida albicans* were grown from all specimens.

Dr. I. W. Whimster: The histology of this lesion is epithelial hyperplasia of eczematous type with underlying œdema and inflammation. Growing in the partly keratinized layer of the epithelium and invading down to the level of living cells is a fungus, morphologically *Candida.*

I have seen several other cases with a similar clinical and histological type of lesion in the mouth, accompanied by similar invasion by a morphologically similar fungus. I have examined alarge series of other types of hyperplastic lesion in the mouth and have been unable to demonstrate any

similar fungal invasion. I therefore suggest that in the present case the fungus may be acting as a pathogen. It will be interesting to learn whether this organism is part of the normal flora behaving in an abnormal way or whether it is a foreign organism.

Dr. R. W. Riddell: The appearance of the invasive fungus in Dr. Whimster's sections stained by periodic acid Schiff method is strongly suggestive of *Candida* (*Monilia*) *albicans*. This organism is, of course, a normal inhabitant of the mouth but is usually non-invasive. It would seem to be very significant that Dr. Whimster has failed to find this appearance in hyperkeratotic tissues of tongues in a large number of other conditions. Monilial glossitis has been described as frank thrush and as a chronic infection giving rise to a smooth tongue with scattered white lesions. I cannot recall having seen this tumour-like process described in relation to invasion by this organism.

Hodgkin's Disease with Collagenous Nodules.—N. A. THORNE, M.D., M.R.C.P. (for BRIAN RUSSELL, M.D., F.R.C.P.).

History.—Eighteen years ago Mrs. F. T., aged 50, developed angioneurotic œdema, at first involving the periorbital tissues, face and neck. The attacks usually began four to five days before a menstrual period and persisted for about a week. Twelve years ago angioneurotic œdema began to spread to the arms and legs, the latter often being œdematous while the facial involvement became less severe. Six years ago swollen glands appeared in the neck and then in the axillæ, the neck glands later diminishing in size. Three years ago swellings developed below both groins. Since then she has noticed lumps in both groins and the swelling below the right groin frequently enlarges "like a bag of water". During the last three years a persistent, irritable eruption has appeared on the legs: there have also been a few discrete lesions on other parts of the body. Her general health has remained good throughout.

Past and family history.—Not relevant.

On examination.—Pulse, temperature and respirations normal. A well-nourished woman with no anæmia.

Skin: An infiltrated, slightly scaly erythema of both legs with some lichenification. There are several flat, yellowish nodules present on these areas.

Generalized lymphadenopathy, including enlarged intra-abdominal lymph glands. The liver is enlarged 3 in. below the right costal margin and the spleen can be distinctly felt 1 in. below the left costal margin.

On the upper and inner aspect of the right thigh there is a "scrotal-like" sac containing an irregular, hard, freely mobile mass: two similar masses are present on the opposite thigh.

Other systems: No abnormality. Urine: No abnormality.

Investigations.—Blood count: Hb 84%, white cells 14,100 (34% polymorphs, 51% eosinophils, 9% lymphocytes and 6% monocytes). Red cells and platelets normal.

X-ray of chest: No abnormality.

X-rays of skull, lumbar spines and humeri: No evidence of myelomatosis.

Plasma proteins: Total 7·6 grammes per 100 ml., albumin, 3·3 grammes per 100 ml., globulin 4·3 grammes per 100 ml.

Urine: No Bence-Jones protein present.

Histology (Dr. J. W. Landells).—Axillary lymph node: Lymphohistiocytic hyperplasia, probably inflammatory, of a fragmented axillary lymph node. Inguinal lymph gland: Inguinal lymphatic enlargement, though extreme, can probably be ascribed to chronic inflammatory changes, in view of the prolonged skin condition. The plasma cell count in the gland is high, and suggests hyperglobulinæmia; in view of this the possibility arises that the hepatomegaly and splenic enlargement are due to amyloidosis.

Histology (Dr. D. J. O'Brien).—Skin of left leg: Diffuse moderately heavy dermal infiltration by large mononuclear cells, plasma cells, and a few eosinophils, which is suggestive of a reticulosis. Skin of right leg: The centre of this nodule is composed of stout acellular collagen; in its periphery there is moderate focal and slight diffuse infiltration of lymphocytes and eosinophils.

ADDENDUM: The slide showing stout acellular collagen was shown at the meeting of the Section of Dermatology on 18.3.54 together with a section obtained by liver biopsy which revealed infiltration with eosinophil leucocytes, most marked above the portal system. There was no evidence of amyloidosis in this or the previous sections.

Dr. P. D. Samman: This is a fascinating case but I cannot see any justification for calling it Hodgkin's disease.

Dr. J. O. Oliver: I agree with Dr. Samman. I could not see any justification for regarding this as a case of Hodgkin's disease.

Dr. Brian Russell: There is a long history of hypodermal urticaria, followed by enlargement of the lymph nodes, liver and spleen, marked eosinophilia, and a polymorphic cellular infiltrate in the dermis. Hodgkin's

disease seems the most probable diagnosis unless one is prepared to call the condition "eosinophilic leukaemia" in view of the 51% of eosinophils (7,200 per c.mm.) in a total white cell count of 14,100 per c.mm.

Dr. R. E. Bowers: Are these masses radio-sensitive?

Dr. Thorne: Radiotherapy has not been given a trial.

Dr. L. Forman: I would agree that there is no positive evidence of Hodgkin's disease. This patient's history suggests that she has developed an allergic sensitivity with manifestations in the connective tissue and glands. I would suggest that she might show amyloid in the skin.

Dr. Thorne: Our pathologist found no evidence suggesting amyloidosis in the hæmatoxylin and eosin sections.

Chromoblastomycosis.—K. D. CROW, M.B., M.R.C.P., and R. W. RIDDELL, M.D., F.R.C.P.

Mr. W. G., aged 36.

History.—The patient is a West Indian Negro who has been living in England for the past two years. Before leaving Jamaica he had always been an agricultural worker.

For the last twelve years he has had a lesion on the right elbow which has been very slowly increasing in size. He cannot remember whether the onset was preceded by an injury but he was working on a farm at the time.

On examination.—There is a horse-shoe shaped lesion on the point of the right elbow about three inches across with central scarring and, at the periphery, infiltrated lesions with thick, silvery scaling crusts (Fig. 1). If these are removed a dry, slightly raised, red, granulomatous surface is revealed. The lesion has always been dry, is not painful, and does not itch.

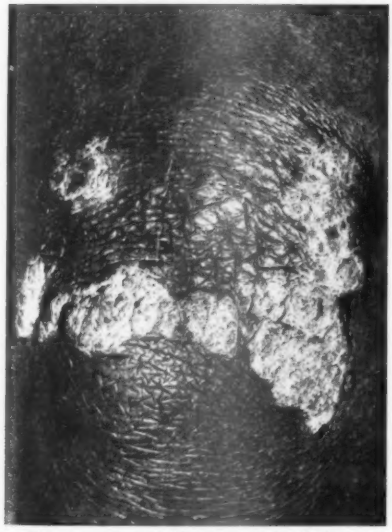

FIG. 1.—Chromoblastomycosis of elbow.

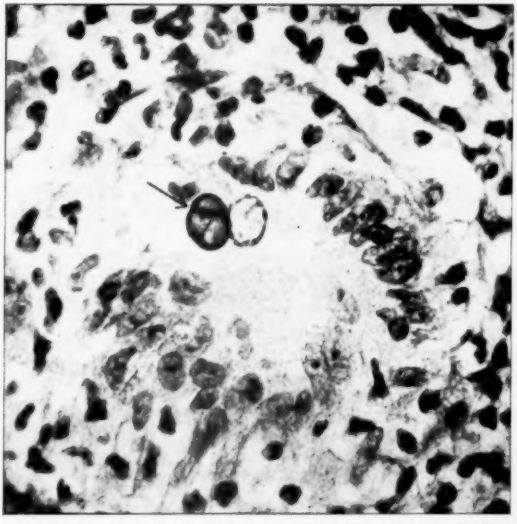

FIG. 2.—Section of granuloma showing fungous bodies within a giant-cell (arrow). Stained by hæmatoxylin and eosin. (× 1,370.)

General examination revealed nothing of significance.

Investigations.—W.R. negative.

Histology (Dr. I. W. Whimster): There is epidermal hyperplasia with underlying severe chronic inflammation. There are numerous tubercle-like structures present and in these, and in giant cells, there are brown, spherical bodies (*see* Fig. 2).

Potassium hydroxide preparation of skin scrapings: Numerous mulberry-like clusters of brown, spherical fungous bodies were seen.

Mycology: *Hormodendrum pedrosoi* isolated (*see* under Discussion).

DISCUSSION

It should, perhaps, be stressed that this disease is unrelated to North or South American blastomycosis; only one case of the former condition has been reported in Britain (Dowling and Elworthy, 1925).

Chromoblastomycosis was discovered in Brazil in 1911, but a description of this first case was not published until 1920 (Pedroso and Gomes). The patient had nodular and ulcerated lesions of the foot and leg; brown bodies were seen in biopsy sections and a dark coloured fungus was isolated. Medlar (1915) reported another case of the disease from Boston, and the fungus isolated was called *Phialophora verrucosa* in view of the cup-like sporing structures it produced and the type of lesion from which it was grown. In 1922, Pedroso's original culture was restudied and was found to produce not only phialophora spores but hormodendrum (spores in branching chains) and acrotheca (terminal spore clusters) types as well; it was named *Hormodendrum pedrosoi*. Finally, Carrion

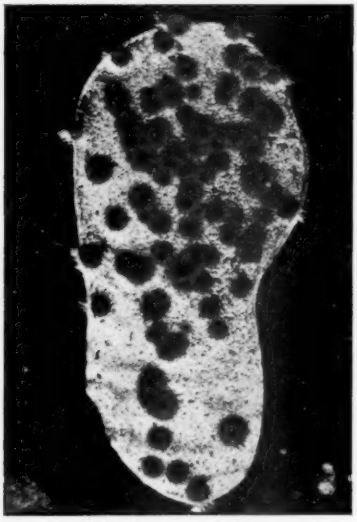

FIG. 3A.

FIG. 4B.

FIG. 3.—(A) Colonies of *Hormodendrum pedrosoi* grown from ground-up biopsy tissue; three-weeks old culture on Sabouraud's medium (× 2). (B) Black coloured reverse to colonies.

(1936) in Puerto Rico, who has since made classical studies upon this disease, described a third organism (*Hormodendrum compactum*). The three fungus species may be roughly summarized as follows:

	Hormodendrum spores	Acrotheca spores	Phialophora spores
H. pedrosoi	Numerous	Numerous	Few to moderate
P. verrucosa	Absent	Absent	Numerous
H. compactum ..	Numerous and compact	Moderate	Scanty

Hormodendrum pedrosoi is much the commonest causative species and usually produces disease in tropical and subtropical countries. *Phialophora verrucosa* is a rare cause and has tended to be found in temperate areas. *Hormodendrum compactum* has been isolated on only two occasions.

Since the vast majority of reported lesions have occurred on the legs of agricultural workers, especially in those working bare-footed, it would be reasonable to assume that these fungi are normally present in the soil. This, however, has not been verified. Some cases on record had received injuries from wood at the sites of their initial lesions. Isolations of *P. verrucosa* from wood-pulp have been reported. Gomes, too, has described an infection resulting from injury by wood of a eucalyptus tree; similar organisms were isolated from the lesion and from the tree in question.

Once these fungi are introduced by trauma into the skin they develop into small round brownish bodies which reproduce by segmentation (Fig. 2). Their growth is greatly restricted and colonies do not develop unless they are transferred to a culture medium. In the present case, excised tissue was cut into small fragments and some of these were planted on Sabouraud's medium. The remainder were ground-up to give a concentrated suspension in Sabouraud's broth; this was also seeded on to plates of the medium. Dark coloured colonies, black on reverse, grew after three weeks at 26° C. (Fig. 3A and B) and were identified as *H. pedrosoi*. (A final detailed mycological report from the Institute of Dermatology will be published separately.) This species was also implicated in the one other Jamaican case on record (Shoucair *et al.*, 1952).

Histologically, the lesions of chromoblastomycosis may closely resemble almost any of the chronic granulomata. They may persist for forty years or more, but occasionally undergo spontaneous healing. The process is essentially benign, remaining confined to the skin and never involving underlying structures, such as muscle or bone, or metastasizing to viscera.

The most satisfactory form of treatment, whenever practicable, would seem to be excision and skin-grafting; this is contemplated for this particular patient.

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MEDLAR, E. M. (1915) *J. med. Res.*, **32**, 507.
PEDROSO, A., and GOMES, J. M. (1920) *Ann. paulist. Med. Cir.*, **11**, 53.
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The following cases were also shown:

Nævus Anæmicus (Voerner).—Dr. I. MARTIN-SCOTT.

Incontinentia Pigmenti (Bloch-Sulzberger Anomaly).—Dr. E. J. MOYNAHAN.

Ainhum.—Dr. R. V. GRANGE (for Dr. BRIAN RUSSELL).

Leprosy.—Dr. D. I. WILLIAMS.

(1) Acrosclerosis. (2) Bullous Pemphigoid.—Dr. R. T. BRAIN.

[These cases may be published later in the *British Journal of Dermatology*.]

[*March* 18, 1954]

Recurrence of Lupus Erythematosus in Skin Graft.—J. E. M. WIGLEY, F.R.C.P.

Mrs. E. W., aged 52.

This patient has had lupus erythematosus for many years, and the butterfly area, which evidently was affected, was excised in 1940 and grafted.

The visible recurrences began about two years ago, and appear to be responding somewhat to the use of mepacrine in 100 mg. doses daily.

Fig. 1 shows the disfiguring, dead-white scarring, the bilateral ectropion and the recurrences in the right lower eyelid and on the tip of the nose.

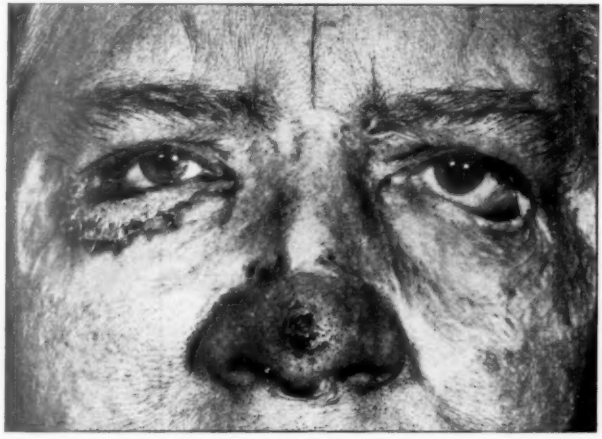

FIG. 1.

Dr. L. Forman: I know of a young girl with a patch of discoid lupus erythematosus on her cheek who became extremely ill after the area was excised.

Dr. A. C. Roxburgh: I remember a similar case treated by radium. The nose was re-made by a plastic surgeon and then the new nose became affected.

The President: I think some plastic surgeons do not differentiate the two types of lupus. While excision may be used for localized lupus vulgaris, nothing but trouble seems to have come out of the cases in which lupus erythematosus has been excised and grafted.

Dr. Wigley: I think we must exonerate the surgeon this time. I understand he was asked to remove it and he did what he was asked.

? Necrobiosis Lipoidica Diabeticorum of the Scalp.—LOUIS FORMAN, M.D.

Mrs. K., aged 69.

History.—Falling of hair and crusting of the occipital scalp and adjoining vertex. The area has slowly extended over five years. She has been treated for mild diabetes and hypertension with a diet.

On examination.—There is an area, longest axis 15 × 11 cm. scarred and hairless save for a central tuft of hair (Fig. 1). The bordering rim shows a brown translucence which a year ago measured 1 cm. (Fig. 2). At other sites the rim is scaling or crusted. Just within the rim are numerous yellow islands, probably of fat, showing through the scar.

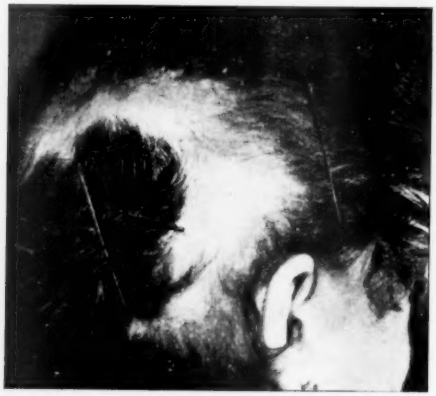

FIG. 1.—Atrophy of the scalp with central tuft of hair.

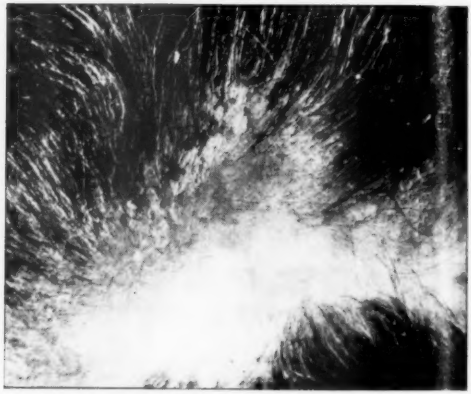

FIG. 2.—Brown translucent and scaling border.

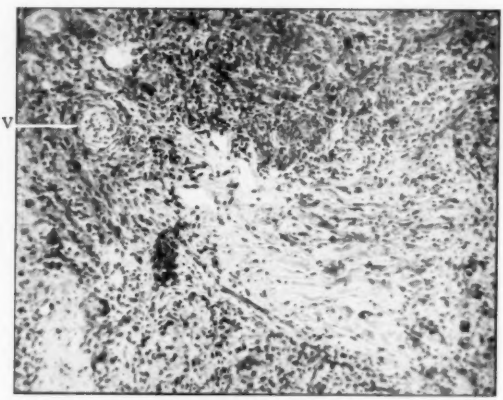

FIG. 3.—Central area of altered collagen, surrounding granuloma and obliterated vessels (V). (× 70.)

Investigations.—Blood pressure 200/100, W.R. and Kahn negative. X-ray of chest negative. The blood sugar curve was of a severe diabetic. Fasting 225 mg.%; 1 hr. after 50 grammes of glucose 416 mg.%; 2 hr., 420 mg.%; 3 hr., 256 mg.%.

Section of the translucent edge shows areas of altered collagen, staining poorly and fragmented, surrounded by a rim of granuloma containing numerous giant cells of the foreign body type, histiocytes and fibroblasts (Fig. 3). A feature of the section is the altered blood vessels in the immediate neighbourhood of the degenerating collagen.

The vessels show hyalinized walls with infiltration by lymphocytes and histiocytes and obliteration of the vascular channels. The changes are similar to those demonstrated in the necrobiosis lipoidica of diabetics.

Treatment.—Her previous treatment, given abroad, included 8 injections of Spirobismol (10% suspension of quinine iodobismuthate) and 8 injections of ACTH. This had to be discontinued because of the hypertension. She also had an undetermined amount of aureomycin. I gave her isoniazid 300-400 mg. a day for four months and 10 grammes of 2·5% hydrocortisone ointment over two weeks to one area, and 30 grammes of potassium iodide a day for five weeks without definite improvement.

Comment.—Dr. H. Haber and Dr. S. De Navasquez after examining the slides suggested a chronic granuloma, either tuberculosis or sarcoidosis. The lack of response to isoniazid in adequate dosage would discount the suggestion of lupus vulgaris. Again, sarcoidosis should be improved by ACTH. In my view the massive collagen affection and the obliterated and organized vessels in a diabetic with hypertension suggest a necrobiosis lipoidica diabeticorum.

Dr. F. F. Hellier: At first sight this case has many similarities to lupus vulgaris. The infiltration and the curious brownish colour are typical but the site and the progress are very much against it being lupus. It took five years to cover the area and the condition has not responded to treatment. Thinking it over—I just throw this out as a suggestion—the histology is rather more granulomatous than the ordinary necrobiosis and I wondered if it could be related to "granuloma disciformis atrophicans" of Miescher. This has a somewhat similar appearance of a completely atrophic area with a surrounding granulomatous margin.

Dr. J. R. Simpson: Five years ago I saw a similar case. It had these particular yellow patches. I thought it was lupus vulgaris and I treated the patient with calciferol. She developed lesions elsewhere resembling lupus vulgaris and on biopsy it showed the histology of tuberculosis. There has been some improvement.

Dr. D. S. Wilkinson: I have two patients with a picture of necrobiosis—or perhaps, rather of granulomatosis disciformis—in whom the lesion started at the same time as general symptoms which have led to a diagnosis of sarcoidosis. The histological picture shows the usual difficulty of interpretation but I feel that this case perhaps falls into the same group.

Dr. S. C. Gold: I would support Dr. Wilkinson's suggestion that this condition is sarcoidosis. I have recently seen a similar case which was originally shown by Dr. J. H. Twiston Davies in 1952 at a meeting of the North of England Dermatological Society as lupus erythematosus of the scalp. Subsequently this patient had developed typical sarcoid lesions elsewhere on the skin, confirmed histologically, as well as pulmonary sarcoidosis. The clinical appearance of yellow, waxy atrophy with telangiectasia so similar to necrobiosis lipoidica was identical in my patient.

Dr. H. T. Calvert: This patient's lesion is exactly the same as that of a case shown on January 24, 1953, at a meeting of the Oxford Regional Dermatological Society. There was the same ring form.
The consensus of opinion was that it was a sarcoid. The histology was the same.

Dr. D. I. Williams: In "necrobiosis", there is atrophy and scarring in the centre of the lesion; in this case the centre is largely spared by the disease. Will someone say why?

Dr. J. E. M. Wigley: I was wondering if the question of a syphilitic lesion has been ruled out. I know she has a negative Wassermann. Would potassium iodide meet the case?

Dr. Forman: I am interested to hear that so many people have seen cases exactly like it, as I thought it was somewhat unusual. The differential diagnosis would include lupus vulgaris and erythema annulare. I would say there is sclerosis, not just atrophy. I do not think it is likely to be lupus vulgaris because I do not think the histology would fit, nor would the histology fit in with sarcoidosis. There was no response to isoniazid. She has not been given calciferol in view of her age and her blood-pressure. Dr. Wigley's comment is very apt indeed although the Wassermann and Kahn tests were negative but she has had eight injections of bismuth iodide compound.

An Unusual Intra-epidermal Carcinoma.—Louis Forman, M.D.

Fig. 1 shows a defined area over the right breast, present for eighteen years in a woman aged 65. The area was 11 cm. in diameter, dry and warty in parts, with small crusts elsewhere. The areola was affected on one side but the nipple was not involved. The breast was normal and there were no enlarged glands. The breast was removed as the only practical treatment by Mr. D. H. Patey and no change was found macroscopically or microscopically in the breast tissue by Dr. A. C. Thackray. The patient remains well after four years.

Sections of the affected skin showed regularly disposed islands of altered cells. The normal epithelial cells are pressed to one side (Fig. 2). Examination of many sections suggests that some of these islands of clear pale cells are arising from or in the neighbourhood of darker staining, smaller and more closely packed epidermal cells. Further, the altered foci of cells can in some sections be seen to form granules of keratohyaline and to assume a concentric arrangement as though there is an endeavour to produce a keratinized pearl.

Fig. 2 shows defined islands of malignant epidermal cells producing keratohyaline granules.

Fig. 3 shows islands of cells apparently in the process of being cast off. Notice the epidermal cells around are small and darkly stained, ? representing another phase of the intra-epidermal carcinoma.

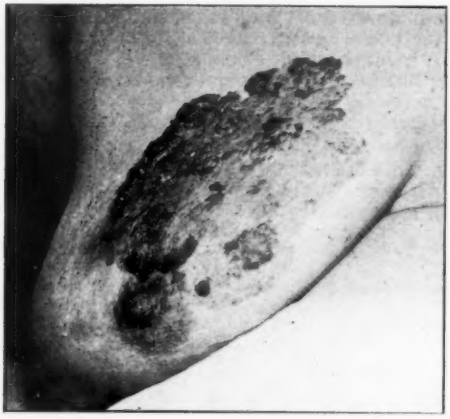

FIG. 1.

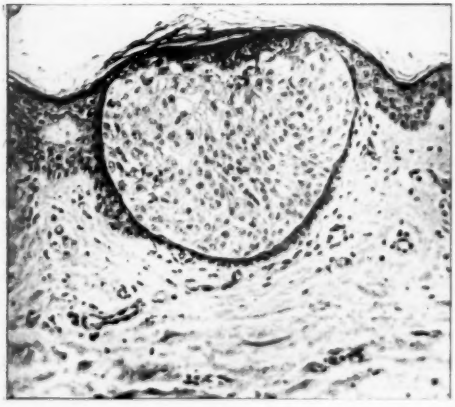

FIG. 2.

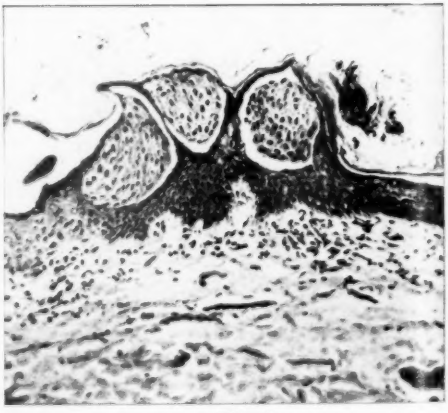

FIG. 3.

Dr. Peter Smith: I have recently seen an almost identical case. This was in a man, aged about 60, with carcinoma of the bronchus and cutaneous metastases of a few weeks' duration, in the left thigh. In the groin, quite close to the metastases, there was a warty hyperkeratotic plaque of many years' standing. When I saw the section from this lesion I was reminded of the slide of Dr. Forman's case which I had seen in the United States three years ago. Because of its most unusual appearance it had been sent by Dr. W. Freudenthal to Dr. Stephan Epstein in Marshfield, Wisconsin. At that time the histology was thought to be different from that of the lesions described by Borst and Jadassohn.

Dr. H. Haber: During the last few years I have come across quite a number of lesions showing histological features similar to those seen in the section shown by Dr. Forman. Clinically they represent small or larger tumours simulating keratomas, warts, seborrhœic warts or even melanomata. In any case a clear-cut clinical diagnosis was hardly ever offered. Histologically these lesions show peculiar intra-epidermal changes, quite distinct from the usual changes in other intra-epidermal epitheliomas. There are islands of cells more of the basal-cell character arranged in whorls, sometimes separated by clefts from the rest of the epidermis, looking like segregated nævus cells in a junctional nævus. Some lesions show these groups of cells to have a tendency to undergo keratinization, looking in that case like intra-epidermal squamous-cell epitheliomas. I think these lesions belong to the so-called intra-epidermal epitheliomas as described by Borst and Jadassohn. Whether they are true epitheliomas or late intra-epidermal nævi one cannot tell. (*See* Ormsby, O. S., and Montgomery, H., 1948, Diseases of the skin. 7th ed. London; p. 826.)

Dr. **I. Martin-Scott:** Dr. Smith kindly showed me this section some time ago. It seemed to me that these islands of tumour cells started as an intra-epidermal focus and appear encapsulated by the squashed prickle cells being pushed aside. In some places they seemed to be due to an overgrowth of sweat duct cells lying within the epidermis.

Dr. **I. W. Whimster:** This is one of the types of pre-tumorous lesions which occur in people with arsenical keratoses. When they invade they produce tumours which are cytologically similar to their intra-epidermal "cell nests".

Dr. **J. S. Pegum:** What Dr. Smith has said raises the interesting question of whether internal carcinomata can ever metastasize in the epidermis. His case had an internal carcinoma and quite recently I saw an intradermal carcinoma the pathology of which was very much like the Borst-Jadassohn carcinoma shown by Dr. H. Haber to the Section on a previous occasion (1953, *Brit. J. Derm.*, **65**, 321). My case had carcinoma of the bronchus.

Reticulosis with Localized Alopecia.—J. S. Pegum, M.D.

J. H., female, aged 57.

History.—January 1950: Herpes zoster over right lumbar region and groin. May 1952: Intense itching and redness of the left axilla and of the groins. July 1952: Boils in the perineum and one axilla. January 1953: Boils cleared: noticed a firm swelling like a sorbo-rubber ball in the right groin, the skin over which was raw, red and tender. March 1953: Similar swelling in the left groin. April 1953: Soft swelling, irritation and loss of hair over the occiput, with subsequent spread to other parts of the scalp. Lumps appeared in the neck and behind left ear. August 1953: Admitted to the London Hospital. Localized alopecia over vertex and occiput, associated with boggy infiltration, weeping and scaling. Exudative dermatitis of the axillæ. Elongated bolster-like swellings of both groins, deep brownish-purple in colour with small ulcer over that in the right groin. Follicular papules over extensor aspects of arms and legs and on back. Enlarged rubbery lymph glands in the neck. October 1953: Discharged from hospital, clinical improvement following local measures. November 1953: Readmitted to hospital, following exacerbation of scalp lesions with exudation and development of boggy exudative lesions over back of neck and bolster-like tumid swelling behind right ear. Given superficial X-ray treatment to right groin and behind neck with regressions of lesions. Scalp became dry and healed with local measures. Most areas of alopecia persisted: one or two showed regrowth: two became more extensive.

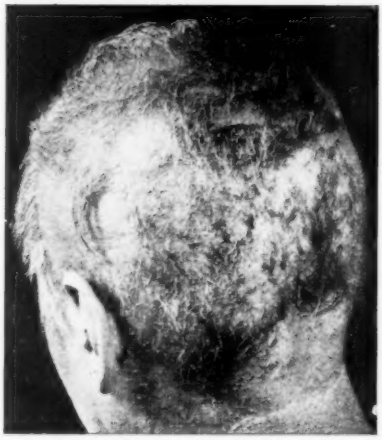

Fig. 1.—Reticulosis with localized alopecia.

Present condition (16.3.54).—Scalp (Fig. 1): Patches of localized alopecia rounded and well defined. The skin over the patches is either normal or slightly scaly, but is infiltrated on palpation. The empty follicles have either a small ring or plug of scale and a surrounding halo of brown translucency. The most recent patch in the left temporal region is raised and the skin over it is red, shiny and tense. Body: On the elbows, shoulders and buttocks there are perifollicular papules and follicular horny spines. In the left groin there is a tumour 6 cm. by 3 cm. covered with pink skin, part of which is ulcerated and surrounded by a pigmented border. In the right groin the tumour has disappeared, leaving an area of pink skin with a pigmented border. Glands: In the left posterior triangle there is an enlarged lymph gland, rubbery in consistency and mobile.

Investigations.—Blood count (13.11.53): Hb 89% (13·2 grammes per 100 ml.). W.B.C. 9,100 (polys. 60%, eosinos. 19%, lymphos. 16%. monos. 5%). X-ray of chest (1.9.53): No abnormality. W.R. (8.9.53): Negative.

Histology.—Cervical lymph gland (25.9.53) (Dr. D. J. O'Brien): "Non-specific reactive inflammation in cervical gland. Large numbers of plasma cells and areas of reticulum cells; but there is no evidence of disorganization of structure or a reticulosis." Skin from right groin (7.9.53): Horny layers in part absent, in part parakeratotic. Prickle-cell layer: acanthotic, with downward proliferation of "rete pegs" and thinning over the tips of the papillæ. Melanocytes can be seen in relation to the basal layer, with ramifying dendrites. Sparse to moderate infiltration with polymorphs, mononuclears and eosinophils. Dermis: Profuse infiltrate with many eosinophils and mononuclears; lesser number of plasma cells and epithelioid cells; and occasional giant cells.

Skin from scalp (17.9.53): Horny layer: absent or parakeratotic. Dermis: Absent hair; few hair follicles, and these appear to be disintegrating. Numerous smooth muscle elements show vacuolation. Moderate infiltrate in upper third, massive in lower third in relation to hair follicles, made up of eosinophils, mononuclears and epithelioid cells.

Comment

The following features are of interest:

(1) The alopecia is localized in rounded areas. It resembles superficially alopecia areata but differs in that the lesions are a little raised above the surface, are infiltrated, and are slightly scaly with small scales or horny rings in the mouths of the empty follicles. Each of the follicles is surrounded by a brown translucent halo, as if it had its own private granuloma sheath surrounding it. Exclamation mark hairs were not seen.

(2) The bolster-like tumours in the groins and behind the right ear.

(3) The areas of follicular keratosis which resemble those in the case of reticulosis presented by Sneddon (1953). When I first saw this patient I thought Hodgkin's disease was the most likely diagnosis, but some of the glands have since involuted and now I wonder whether mycosis fungoides is not a more likely diagnosis, in view of the tumours in the groins, and also because alopecia is commoner in mycosis fungoides than in Hodgkin's disease. With regard to treatment, the groin tumour which was treated proved to be remarkably radio-sensitive, and I am now wondering whether radiotherapy to the scalp would not produce the therapeutic paradox of hair regrowth.

REFERENCE

Sneddon, I. B. (1953) *Proc. R. Soc. Med.*, **46**, 546.

Dr. I. B. Sneddon: This case is very much like one I showed last year (1953, *Proc. R. Soc. Med.*, **46**, 546; *Brit. J. Derm.*, **65**, 412) although it did not then show alopecia. Since that time patches of alopecia have appeared all over the patient's head. The patient has gone downhill very rapidly and has not responded to any treatment.

The following cases were also shown:

Poikiloderma.—Dr. H. R. Vickers.

Poikiloderma Forme Fruste.—Dr. I. B. Sneddon.

"Permanent Freckles".—Dr. R. E. Bowers.

Prurigo Nodularis.—Dr. R. T. Brain.

Porphyria Cutanea Tarda.—Dr. Stephen Gold.

Lichen Amyloidosis.—Dr. R. H. Meara.

Sarcoidosis under Treatment with Cortisone.—Dr. D. S. Wilkinson.

Lichen Planus in a Child.—Dr. K. V. Sanderson (for Dr. R. T. Brain).

Congenital Ectodermal Defect.—Dr. K. V. Sanderson.

[These cases may be published later in the *British Journal of Dermatology*.]

Section of Otology

President—R. R. SIMPSON, F.R.C.S.Ed.

[*February* 5, 1954]

MÉNIÈRE'S DISEASE

Mr. Terence Cawthorne and Dr. A. B. Hewlett (London):

INTRODUCTION

After we have learned to walk we expect to be able to move freely in an environment which is solid and stable. Though we may voluntarily give up this comfortable state, as when we travel by sea or by air, at least we know what to expect. For the patient with Ménière's disease this trust in the behaviour of his surroundings no longer exists. From time to time he has experienced the sensation of movement of his environment or of himself when reason tells him that they should be still. His feeling of security is further undermined by nausea and vomiting, and in addition his distress is increased by deafness and tinnitus. It is not surprising that these symptoms often suggest a widespread disorder involving at least the nervous and digestive systems, but it is now generally agreed that in almost every case the disorder has its source in the internal ear.

Although the syndrome which we now recognize as that of acute labyrinthine failure had aroused the interest of many workers, it was not until 1861 that Prosper Ménière of Paris published a series of papers showing that a disordered labyrinth could cause paroxysmal attacks of vertigo and vomiting associated with unilateral deafness and tinnitus.

Ménière had passed an interesting and not uneventful life during which he had been physician-accoucheur to the wife of the Pretender to the French throne, a friend of Balzac's, and superintendent of a Deaf and Dumb Institution (Wells, 1947), but it was not until the last year of his life that he announced the discovery which was to earn him fame.

After this discovery it became the custom to attach the label "Ménière's syndrome" to cases of paroxysmal vertigo, with or without deafness and tinnitus, no matter what the cause; while in more recent times bouts of vertigo without deafness have earned the sobriquet "pseudo-Ménière's syndrome". Despite this general appreciation of Ménière's discovery the labyrinth guarded its secrets well. More than three-quarters of a century passed before Hallpike and Cairns in 1938 were able to demonstrate a deformity of the endolymphatic system of the labyrinth on the affected side in certain sufferers from what was now called Ménière's disease. They concluded that this appearance was the result of recurrent distension of the endolymphatic system caused by a failure of the mechanism governing the production and disposal of endolymph. They felt that as an anatomical basis for the disorder had been demonstrated it was appropriate to use the term Ménière's disease instead of Ménière's syndrome. Since then several other workers have confirmed their findings and the descriptive subtitle of endolymphatic hydrops is now often used.

There are, of course, other labyrinthine disorders, with vertigo as their principal symptom, which may mimic Ménière's disease but we have found that endolymphatic hydrops is responsible for most cases of aural vertigo.

That the ear was often responsible for vertigo was clearly appreciated by Sir William Gowers, who in 1893, when writing of his experience at the National Hospital for Nervous Diseases, said: "Of 106 consecutive cases in which definite vertigo made the patient seek advice, in no less than 94 ear symptoms were present. . . . It is exceedingly rare for definite vertigo to occur apart from aural symptoms, and it is certain that in the majority of cases in which vertigo has been ascribed to other causes, these have only had an exciting influence, and the symptom has been essentially due to the effect of unobtrusive labyrinthine disease."

Our experience has been the same as that of Sir William Gowers and in Table I it will be seen that out of 1,902 cases of vertigo referred to us in the course of the past ten years, 1,169 or 61% were due to Ménière's disease, and altogether 87% were due to a peripheral labyrinthine lesion.

Although it may be that there are more cases of central vertigo than Table I suggests, it is interesting to note that the proportion of central to peripheral causes where vertigo is the predominating symptom is almost the same in this group as in that of Sir William Gowers.

The central causes include epilepsy, disseminated sclerosis, certain temporal lobe tumours, some tumours in the posterior cranial fossa usually of the cerebellopontine angle or in the mid-line where the vestibular connexions in the cerebellum are involved, and thrombosis of the posterior inferior cerebellar artery. Migraine has also been considered as a cause.

TABLE I.—CAUSES OF VERTIGO IN A SERIES OF 1,902 CASES

Central		130
Peripheral		1,657
Ménière's disease	1,169	
Trauma	137	
Vestibular neuronitis	152	
Positional	130	
Infective	69	
Not classified		115

In the peripheral groups under the heading of trauma are included patients with persistent vertigo following head injuries, and for a more detailed consideration of this group *see* Cawthorne and Cooksey (1946).

Vestibular neuronitis is a condition in which patients suffer a sudden loss of vestibular function, as a rule on one side only, but without any impairment of hearing. Dix and Hallpike (1952) who first used the term vestibular neuronitis, believe that the lesion lies somewhere in the vestibular neurones, and it may be situated either in Scarpa's ganglion or more centrally. It may be associated with a focus of sepsis or may accompany a respiratory infection, though in many cases there is no obvious causal factor. This may well be the condition which is known as "epidemic labyrinthitis".

Paroxysmal positional vertigo can be due either to a lesion in the utricle as shown by Dix and Hallpike (1952), or it may accompany lesions involving the vestibular connexions in the cerebellum. In the peripheral cases the vertigo and nystagmus appear some seconds after the head has been placed in a certain position, usually backwards, and to one side. The vertigo and nystagmus last a few seconds—rarely more than ten—can be fatigued easily by repetition and do not reappear for at least half an hour even when the offending position is resumed. It may sometimes follow a head injury. In the central cases, the vertigo and nystagmus are not fatigable and the direction of the nystagmus may vary with the position of the head. In some of the central cases the sensation of vertigo is slight but on the other hand we have seen a few cases in which the vertigo was intense and was accompanied by vomiting.

Further information about these two interesting groups of aural vertigo which are sometimes confused with Ménière's disease can be obtained from an outstanding paper by Dix and Hallpike (1952).

The infective group includes patients in whom past or present middle-ear infection has resulted in an erosion of the bony labyrinth or where an opening has been accidentally made in the course of an operation for infection.

There is an interesting little group of patients in this infective series who exhibit what appears to be a functional disturbance of balance often with a bizarre gait. The connexion between the labyrinth and the clinical picture may not be obvious and in fact is not infrequently overlooked. There may have been a former mastoid operation now well healed, but for some reason or another there is a slight but continuing fluctuation of vestibular activity. This may be due to a fistula in the bony labyrinth, and there may be depression of vestibular function of the affected side though it is never absent. We have been in the habit of using the term perilabyrinthitis for this group of cases. By destroying the offending labyrinth, we have been able to restore to an active life several patients who had been literally crippled by this complaint. In this connexion we must mention the effect of recurrent bouts of vertigo upon the psychological state of the sufferer. In many patients repeated attacks of vertigo for which no cause is readily demonstrated can easily induce a feeling of insecurity which may masquerade as a psychological disorder. In such patients it is important not to fall into the trap—not infrequently set by the patient or his relatives—of attributing the "attacks" to "nerves" when in reality the "nerves" are due to the "attacks".

Now that we have referred to the problem of aural vertigo in general we would like to enquire a little more fully into the incidence, and clinical features of Ménière's disease, and then to consider the possible underlying causes of the disorder; and finally to discuss the various forms of treatment.

CLINICAL FEATURES

General incidence.—There are many and varied views on the incidence of Ménière's disease, and our own impression has been that it is not so rare as is sometimes believed; though of course we have always appreciated that our experience would not give a true impression of the incidence.

There is, however, now to hand a most informative monograph by the General Register Office on General Practitioners' Records (Logan, 1953). This is an analysis of the clinical records of eight practices with a population of 27,365 persons made during the year ending March 1952.

From this we have chosen five disorders including Ménière's disease which are comparable in frequency (Table II).

Thus it will be seen that while it is not among the commoner group of diseases, it is encountered and diagnosed more frequently than might be expected from the attention given to it in the past. It is now grouped by the General Register Office under "Diseases of the Ear".

There is a slight preponderance of males over females in about the same proportion as was noted in a previous review of 424 cases (Cawthorne, 1947), most of which are included in the present series (Table III). This suggests that, although the preponderance of males is slight, it is consistent. However, women at the menopause tend to attribute symptoms of giddiness to "the change", and therefore they may not always seek advice. As a result of this attitude the predominance of males may be unreal.

TABLE II.—DISORDERS OF COMPARABLE FREQUENCY WITH MÉNIÈRE'S DISEASE IN 27,365 GENERAL PRACTICE PATIENTS DURING ONE YEAR

Scarlet fever	45
Ménière's disease	43
Hyperplasia of prostate	27
Thyrotoxicosis	26
Nephritis and nephrosis	19

TABLE III.—SEX INCIDENCE IN 900 CASES OF MÉNIÈRE'S DISEASE

Male	489
Female	411

Table IV shows quite definitely that the majority of patients (65%) have their first attack before the age of 50.

The disease does not favour one ear more than the other, and in 13% both ears were affected (Table V). It was interesting to find that in half of this bilateral group both ears were obviously affected from the onset of the disorder. In the other half, the second ear was not affected until some years after the first. In one patient the interval was thirty-seven years.

TABLE IV.—AGE AT ONSET OF FIRST SYMPTOM IN 900 CASES OF MÉNIÈRE'S DISEASE

Age group	Up to 25 years	26–50 years	51–75 years	over 75 years
Number of patients	63	521	307	9

TABLE V.—LATERALITY IN 900 CASES OF MÉNIÈRE'S DISEASE

Left ear	408
Right ear	371
Both ears	117
No record	4

It has been held by some that the deafness usually precedes the bouts of vertigo, while others have postulated a different disease when the vertigo precedes the deafness. We do not attach any significance to the order of appearance of the symptoms and, as Table VI reveals, we found that the commonest state of affairs was for the deafness to be noticed simultaneously with the original bout of vertigo; though in the event of one symptom appearing before the other, deafness was the more likely to be first.

TABLE VI.—ORIGINAL SYMPTOM IN 900 CASES OF MÉNIÈRE'S DISEASE

Deafness first	237
Vertigo first	173
Deafness and vertigo simultaneously	449
No record	41

TABLE VII.—OTHER SYMPTOMS IN 900 CASES OF MÉNIÈRE'S DISEASE

Unconsciousness	30 cases
Diplopia	9 cases
Allergy	41 cases
Former head injury	29 cases

Other symptoms are relatively infrequent in Ménière's disease, and in this series a careful note was made of any unconsciousness, diplopia, allergy or head injury (Table VII). Despite the severity of what might be termed the vagal stimulus, genuine loss of consciousness is very unusual in Ménière's disease. In this series it was noted only in just over 3% of cases; but in all of these, the loss of consciousness was only momentary. Anything more than a fleeting loss of consciousness should always lead to an enquiry into the possibility of epilepsy being present. Diplopia is rare, and again is only transitory, unless the real cause of the attack is disseminated sclerosis.

As an allergic basis has been held responsible for the attacks, and as in a recent monograph Williams (1952) has argued strongly in support of this, it may be worth while going into the matter in some detail. An enquiry was always made by us into the presence of any allergic symptoms such as hay fever, rhinorrhœa, asthma, eczema, or colitis. That such a small proportion—under 5%—have other allergic symptoms is not in favour of this ætiology. Though in individual patients the allergic response tends to be localized in a particular organ, an exceptional dosage of antigen is likely to call forth a response from other organs, and this surely would be expected to occur during severe bouts of Ménière's disease. Some 50% of allergic patients have a positive family history of allergy as compared with 7% of normal individuals. Although no specific note was made of the family history we can call to mind only 4 cases of Ménière's disease in which there was a history of a similar disorder in the family. Lastly, the age of onset of allergic symptoms differs from that of Ménière's disease, being less than 40 years in about 80% of cases while that in Ménière's disease,

in our series, averaged 44 years. In this connexion the state of affairs in migraine, a condition in which an allergic basis seems to have been established, may be noted. Here the age of onset is usually in the first two decades, there is a strong family history, and the attacks tend to die out before the age of 60 years.

An association between Ménière's disease and head injury has been suggested, but here again the number of cases in which a head injury might have played a part is probably not more than might be accounted for by the average incidence in the general population, though it is only fair to say that in at least 3 cases, the symptoms first appeared soon after a head injury.

When we consider the cochlear symptoms more closely (Table VIII), it will be seen that nearly all have some degree of deafness, whilst the majority have tinnitus as well. In a bilateral case, tinnitus is often an important indication as to which ear is in the active stage of the disease.

TABLE VIII.—COCHLEAR SYMPTOMS IN 900 CASES OF MÉNIÈRE'S DISEASE

Deafness	859
Tinnitus	764
Distortion of hearing	402

It is quite common to be told that warning of an impending attack is given by an increase or alteration in the tinnitus. Some patients find that just before an attack their constant tinnitus has added to it a clanging machinery-like noise which may prove very distressing.

Distortion of hearing is a valuable distinguishing feature of endolymphatic hydrops which has been noted in nearly half the patients in this series. It is probable that the incidence of such distortion of hearing is higher than the figure just given, as the significance of this feature of the deafness was not always appreciated in the earlier cases. The distortion is usually noticed for loud, shrill and musical sounds, and it is not uncommon to be told by a patient that, previous to the onset of the disease, he enjoyed listening to music, but that during its active phase he finds it impossible to listen any longer to music on the wireless because of the jarring and discordant effect on his ear. To our knowledge, the only other disorder which may cause distortion of hearing is acute acoustic trauma during the stage of recovery. This distortion may seriously impair hearing so that, after labyrinthectomy, in which the distorted remnant of hearing in the affected ear is destroyed, the patient may volunteer that his hearing is better, and that he can enjoy music and other sounds again. A serious effect of this distortion is to reduce the ability to hear speech much more than the ability to hear pure tones. This is well shown in Fig. 1, in which it will be seen that, although there seems to be a potentially useful amount of hearing as measured by the pure-tone audiometer, a speech audiogram reveals that such hearing as remains is of little use for understanding speech.

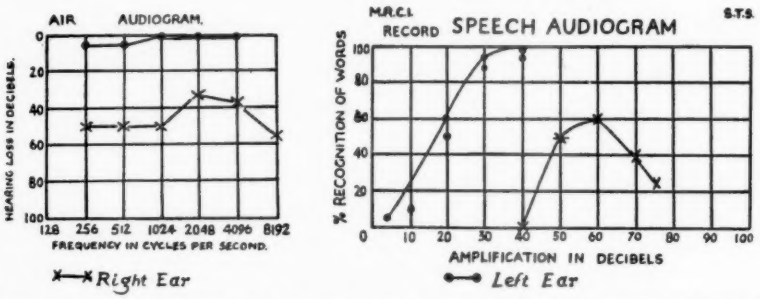

FIG. 1.—Hearing for speech and for pure tones in a case of Ménière's disease. (Reproduced by permission, Cawthorne, T., 1954. In: Modern Trends in Diseases of the Ear, Nose and Throat. Editor: Maxwell Ellis. Butterworth and Co. Ltd.; p. 31.)

The pure-tone audiogram shows the threshold hearing for certain pure tones, while the speech audiogram measures the percentage of words repeated correctly against the loudness of the speech. Normally and in many forms of deafness the louder the speech the better it is understood, but in Ménière's disease there may be but little difference in loudness between just hearing speech and finding it too loud for clarity or comfort.

We regard distortion of hearing as a valuable clue as to the nature of the deafness; and in a certain proportion of cases in which the vestibular signs are not prominent, it is possible to make a diagnosis of endolymphatic hydrops on the cochlear symptoms and signs alone.

The deafness in Ménière's disease is, as would be expected from what we know of the pathology, perceptive, and characteristically affects the lower tones. In the few cases in which there was an

overlying conductive deafness there was also an underlying internal ear condition which was responsible for the attacks.

It is noteworthy that in only one case out of 900 was there clear evidence of a blocked eustachian tube; though we would not deny that this may be occasionally associated with giddiness of mild degree.

Associated ear diseases include congenital deafness and mumps deafness. Although the number of patients in whom Ménière's disease developed in an ear previously affected by mumps is small, there may be a connexion because in 2 cases the attacks followed soon after the mumps neurolabyrinthitis.

In addition, mention must be made of the possibility of hydrops developing after the fenestration operation. Shambaugh (1949) has noticed this in a definite proportion of cases, and we have seen it, too, in a small number of patients. In most of such cases, however, the cochlear labyrinth has been mainly affected, and apart from slight dizziness the vestibular symptoms have, fortunately, rarely been pronounced.

A test of vestibular function should always be carried out, as it may give the only physical sign of a disordered vestibular labyrinth. It occasionally happens that the vestibular abnormality is found in the better hearing ear. In such a case further careful enquiry usually brings to light former attacks and bilateral disease is assumed.

We employ the caloric test according to the technique developed at the National Hospital for Nervous Diseases, by Fitzgerald and Hallpike (1942) and the results in Ménière's disease were at that time given by Cawthorne, Fitzgerald and Hallpike (1942). Further experience shows that a reduced response to caloric stimulation on the affected side is the usual finding (Table IX).

TABLE IX.—CALORIC TEST IN 900 CASES OF MÉNIÈRE'S DISEASE

Canal paresis	640
Directional preponderance	75
Combined canal paresis and directional preponderance	108
Normal	51
No record	26

PATHOLOGY

The distension of the endolymphatic system which is the visible relic of Ménière's disease is the result of recurrent bouts of endolymphatic hydrops. Let us for a moment inquire into the natural history of the disease, and see how this can be compared with what we believe may be going on inside the labyrinth. The attacks tend to appear in groups, with intervals of complete freedom. During what may be called the active phase of the disease, when the attacks are likely to take place, there is often a feeling of pressure in the affected ear, and patients may declare that the ear is blocked, or that it feels as though it was "blown up". This blocked feeling, particularly when it is combined on testing with a false negative Rinne may account for the former belief that a blocked eustachian tube was commonly associated with Ménière's disease. There may be increased deafness and tinnitus, and a general feeling of unsteadiness. These symptoms may build up in a crescendo, ending in an attack of vertigo. When the attack subsides the premonitory symptoms may also disappear. Sometimes, however, a residue of symptoms remains over a period of days, weeks, or even months, and during this time a succession of attacks may be experienced, until quite suddenly one day the ear clears and a quiet phase is entered upon. During the quiet phase, the sensation in the ear, the cochlear symptoms, and the unsteadiness are reduced or absent. We interpret this as follows:

In the active phase, there may be a disturbance of the normal balance between the production and disposal of the endolymph which leads to a rise in endolymphatic pressure. At any time during this period there may be a critical increase in the endolymphatic pressure, which if sufficient to squeeze the blood out of the capillaries, will result in an attack, as suggested by Hallpike and Cairns (1938). This obliteration of the capillaries may, at the same time, hinder the production of more endolymph so that the pressure subsides, circulation returns, the attack passes, and function is restored to the labyrinth. So long as the abnormal state responsible for the disturbance of balance between the production and absorption of endolymph continues, the endolymphatic pressure is liable to be kept above normal. During this active phase, the labyrinth is sensitive to any increase in endolymphatic pressure, as Mygind and Dederding (1932) found when they drew attention to the apparent disturbance of water metabolism in sufferers from Ménière's disease. We have also found that during an active phase the patient is very sensitive to anything which tends to favour the retention of fluid within the body (Cawthorne and Fawcett, 1938). During the quiet phase, the normal balance between the production and disposal of endolymph is restored, so that the labyrinth is no longer at the mercy of any factor liable to affect the pressure within it, and apart from any residual deafness and tinnitus the patient feels well.

There is no rule or regularity about these phases. Sometimes the active phase only lasts for the period of a single attack, while at other times it may extend over weeks or months and include several attacks.

A question which has been asked is: Why is distension of the membranous semicircular canal not found when gross dilatation of the scala media and saccule, and to a lesser extent of the utricle, is usual? The answer given by Hallpike and Cairns was that the membrane of the canals was much thicker than that of most endolymphatic structures. In some, rupture of the scala media may occur with relief of pressure but without recovery of function. Such an effect could account for those cases in which a single apparently typical Ménière's attack leads to permanent loss of hearing and vestibular responses.

In the foregoing account of the mechanics of Ménière's disease, we have been relying on Guild's (1927) theory of the formation, circulation and removal of endolymph. So long as we continue to accept this theory, then it would seem that some hindrance to the disposal of the endolymph through the wall of the saccus endolymphaticus must be the most likely reason for the hydrops. However, the work of Lindsay (1947, 1952) suggests that in animals the saccus endolymphaticus can be obliterated without the subsequent development of hydrops, so there must be other routes for the absorption of endolymph.

That ischæmia of regions of the labyrinth is caused by spasm of the internal auditory artery or of its branches, is the contention of those who attribute the disease to allergy. They suggest that as a result of ischæmia damage is done to vessel walls and this leads to transudation of an endolymph of altered character and higher osmotic pressure. In consequence, dialysis of fluid through Reissner's membrane occurs and produces distension of the endolymphatic system.

This hypothesis would fit the histological findings but it would certainly be strange if the vasospasm so persistently favoured one group of vessels, unless there were some anatomical predisposition. Even in migraine in which vasospasm has been proved the attacks show little lateralization, either side being affected at different times.

Much has grown out of the original observation of Sheldon and Horton (1940) that histamine has a favourable effect on the progress of the disease. This was attributed by some to its effect in allergy, and by others to the fact that it caused peripheral vasodilatation, and so increased the circulation within the internal ear. Other vasodilating drugs, such as nicotinic acid and procaine have been used, and Miles Atkinson (1945, 1946, 1949) and Hilger (1950) have advanced attractive and ingenious hypotheses as to how these drugs may act. Before, however, accepting these views, should we not enquire a little more closely into this matter of vasodilatation of the labyrinthine blood vessels? First of all, we are asked to assume that vasodilatation of the labyrinthine arteries will reduce, or in some way disperse, the fluid hydrops in the labyrinth; and then we are asked to assume that certain drugs do indeed produce vasodilatation of the labyrinthine vessels. If, however, endolymph is secreted by the stria vascularis of the cochlea, then surely the physiological response to any increase of blood flow through the secreting organ should be an increase in the amount of endolymph produced.

There is evidence which suggests that the nervous control of intracranial blood vessels differs from that of the rest of the body (Schmidt, 1952), and it has been shown that peripheral vasodilators have a much less noticeable effect on the intracranial blood flow than on the peripheral circulation. In fact, it seems as though CO_2 is the most, if not the only, certain and potent vasodilator of intracranial blood vessels, and we have observed at operations a dilatation of the blood vessels within the bony labyrinth following the inhalation of CO_2. Mygind and Falbe-Hansen (1951) found that in the guinea-pig adrenaline caused a vasodilatation, and histamine a vasoconstriction, of the labyrinthine blood vessels. If this observation is applicable to man, then the influence that histamine sometimes has on Ménière's disease might be explained by vasoconstriction, and not by vasodilatation.

Following up an observation of Hallpike and Cairns (1938), Lempert and his associates (1952) were impressed by the frequent presence of vesicles in the wall of the membranous semicircular canals in material from cases of Ménière's disease. They suggested that these blebs might be due to "a chronic herpetic neuritis of the vestibular labyrinth of toxic or trophic origin". That similar appearances are present in the canals of many labyrinths from those over the age of 40, who have had no symptoms of Ménière's disease, together with the absence of pathological changes in the neurones, is not in favour of this ingenious hypothesis. Recent work at the Lempert Institute (Rambo, *et al.*, 1953), shows that neither the severance of the vasodilator nor yet of the vasoconstrictor nerves to the ear in monkeys has any lasting effect on the blood vessels of the labyrinth. All this suggests that much more work needs to be done before we can accept without question, hypotheses concerning the effect of altering the blood flow through the labyrinth in Ménière's disease. Thanks to Hallpike and Cairns we know the effect on the delicate endolymphatic structures of attacks of Ménière's disease, but of the events which lead up to such attacks we are still ignorant.

Treatment

Treatment may be considered under the headings of sedation, anti-retentional regime, measures to encourage vasodilation of the labyrinthine arteries, removal of foci of sepsis, drainage of the labyrinth and finally destructive procedures.

(*a*) *Sedation.*—All will be agreed that sedation, either by the barbiturates or by certain of the antihistaminics, of which Dramamine and Avomine seem to be the most effective, is a necessary part of the treatment which, though it may not prevent attacks, will often reduce their severity.

(*b*) *Anti-retentional regime.*—During the active phase of the disease, we have often found it to be of great help to reduce the intake of salt and fluid. Strict adherence to a low sodium diet often discourages attacks though some patients find the regime tiresome.

(*c*) *Vasodilatation.*—This is sought either by drugs, such as histamine, procaine and nicotinic acid, or by paralysing the cervical sympathetic nerve (Passe and Seymour, 1948). We have tried repeated injections of the stellate ganglion on the affected side as reported on by Hoogland (1951) using 2% xylocaine. This is a simple procedure which rarely fails to produce a full Horner's syndrome with suffusion of the eyeball and dilatation of the vessels of the tympanic membrane and of other branches of the external carotid. We have not, however, observed in such cases any change in the retinal blood vessels nor of the vessels within the labyrinth at operation. Apart from a transient alteration of the tinnitus in some of the patients we have not noted any definite and lasting benefit as the result of injecting the stellate ganglion. With regard to surgical interruption of the sympathetic fibres going to the internal ear, Mr. Roland Lewis has kindly operated on some of our cases and he tells us that in half of these the attacks of vertigo have either ceased or have been reduced. Though the hearing for pure tones has not improved, the distortion of hearing has been reduced in about one-third of the cases. Tinnitus was relieved immediately in most, and this reduction in the tinnitus was maintained in about one-third. Thus it seems that in most of the cases something happens within the labyrinth as the result of sympathectomy, though the proportion of cases in which there is sustained relief of symptoms is not sufficiently high to make it certain that such relief is not part of a natural remission.

We have had 3 patients referred from elsewhere because of severe vertigo unaffected by sympathectomy for whom labyrinthectomy was needed. Our feeling at present is that until we know more about the effects of sympathectomy upon the labyrinth and upon the patient generally, we must continue to regard it as an experimental procedure, and not by any means a minor one.

In this connexion we must mention section of the chorda tympani for the relief of Ménière's disease. Rosen (1949) has repeatedly advocated this procedure though it is still not clear to us how and why it should help Ménière's disease, and we feel that even more than sympathectomy this should be regarded for the present as an experimental operation. As regards vasodilating drugs, we have not found, except for histamine, which does sometimes seem to have a favourable effect upon the disease, any other of these measures of definite or lasting help. We have never been able to establish any connexion between Ménière's disease and foci of sepsis, though we would add that in certain allied conditions such as vestibular neuronitis and positional vertigo focal sepsis does seem to play a part as Wright (1937) pointed out.

(*d*) *Destructive procedure.*—(i) *Streptomycin*: The vestibulo-toxic properties of streptomycin have been used in Ménière's disease to abolish vestibular function (Glorig and Fowler, Hamberger, Ruedi, Cawthorne). Unfortunately vestibular function on both sides is affected by the drug and if function is lost in both it may well, in older patients, result in a greater incapacity than the disease for which it is given. We therefore feel that if it is to be used at all it should be limited to young people with bilateral disease; an unusual combination.

(ii) *Drainage of the saccus endolymphaticus*: The logical surgical treatment would seem to be the drainage of the saccus endolymphaticus, as first described by Portman (1927). If it can be identified, incision of the saccus may, it is true, allow an excess of endolymph to escape. But in the process of healing there is likely to be some fibrosis in the wall of the saccus which may even further hinder the disposal of surplus endolymph.

(iii) *Destruction of the labyrinth*: The labyrinth can be destroyed either by introducing into it powerful agents of tissue destruction such as alcohol or diathermy, or by simply removing a portion of the membranous labyrinth, usually, for convenience sake, the membranous external semicircular canal.

There is no doubt that alcohol, as first suggested by Mollison (1931) and diathermy, by Day (1943) are effective agents of destruction, but at times they are too effective—as when their destructive properties are allowed to extend beyond the confines of the labyrinth, causing facial palsy. We prefer to abolish labyrinthine function in Ménière's disease by the simple removal of a piece of endolymphatic labyrinth in the manner first described before this Section in 1943 (Cawthorne, 1943). This operation is simple and safe and quite within the competence of any aural surgeon equipped with adequate magnification and a pair of fine "hair-spring" forceps. In Ménière's disease this operation always results in complete and irreversible loss of both cochlear and vestibular function, though this does not apply necessarily to other disorders (Cawthorne, 1949).

(iv) *Nerve section*: Section of the vestibular portion of the acoustic nerve has the advantage that the hearing may be spared, but it is an intracranial operation which is not without risk. We think it should only be advised when the hearing on the affected side is remarkably good.

In many cases the hearing is badly distorted, so that for speech it is useless, and there seems to be no object served in embarking on a serious operation merely to preserve a distorted remnant of hearing.

Table X gives the results of the membranous labyrinthectomy which we practise.

TABLE X.—MEMBRANOUS LABYRINTHECTOMY FOR MÉNIÈRE'S DISEASE

Total operations	288
Healed by first intention	284
Post-operative infection	4
Transient facial paresis..	1

This has been carried out now in 288 cases, and of these 284 healed by first intention, and there was only a slight post-operative infection in 4, which soon yielded to appropriate antibiotic treatment. In one recent case there was a transient facial weakness but otherwise the post-operative course has been quite uneventful, and in none of these cases did the patient ever get another attack of vertigo from the operated labyrinth. In 6% of the patients, however, the other ear subsequently became affected.

CONCLUSION

Ménière's disease, despite its widespread symptoms, is really an otological disorder. The internal ear is at fault, and proof of the true nature of the disease is only forthcoming after a detailed otological examination. The effect of conservative treatment is difficult to assess because of the natural tendency of the disease towards spontaneous remissions. In stubborn unilateral cases, destruction of the affected labyrinth by the simplest and least harmful method at our disposal is the treatment of choice; and in our experience this has been necessary in just over a quarter of the cases we have seen.

Though we still do not know the cause of Ménière's disease, we are now well aware of its effects upon the labyrinth. Despite the cloud of pessimism which surrounds the treatment, we have found that in the majority of the patients who have come under our care it has been possible by one means or another to prevent or subdue the attacks.

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Mr. **Miles Foxen:** *The Use of Streptomycin in Ménière's Disease*

Very many of the victims of Ménière's disease are vastly improved, if not entirely relieved of their symptoms by non-surgical methods of treatment (Discussion, 1950).

Some cases remain which do not respond to simple methods such as vasodilatation, or histamine desensitization, and, of these, a small number are so obviously bilateral as to preclude labyrinthotomy. It is in this group that certain cases suitable for streptomycin treatment are found, and it will be evident that these cases are few and far between. Indeed it would be most imprudent to apply this method of treatment to cases of Ménière's disease which might respond to less dangerous methods.

As far as can be ascertained it was first suggested by Hawkins of the Merk Institute that the toxic action of streptomycin might be utilized in the treatment of aural vertigo, and in 1948 Fowler reported 4 cases which he had treated during the previous year. He used a dosage rate of 4 grammes *per diem* until the total dose of 25 to 33 grammes had been given, and he was well satisfied with the results.

In 1949 Hamberger, Hydén and Koch reported a further series of 4 cases using a dosage rate of 3 grammes *per diem* until a total dose of 90 grammes had been given. 2 of the cases were reported as being successful. In 1951 the subject was reviewed by Ruedi who added a further series of 3 cases, and again in 1951 Hanson published 5 cases. In the latter series streptomycin was given at the rate of only 2 grammes *per diem* until total doses varying from 40 grammes to 76 grammes had been administered and improvement was recorded in every case. At a meeting of this Section in May 1952 (Discussion, 1952) the toxic effects of streptomycin and dihydrostreptomycin on the acoustic and vestibular systems were discussed. Mr. Terence Cawthorne spoke of the use of streptomycin in Ménière's disease, drawing attention to the fact that the toxicity of different batches of streptomycin might vary. In our own literature I have been unable to discover any case reports though I am aware that a number of British otologists have used this method.

The case to be described was treated three and a half years ago and has remained symptom free. At the age of 17 she underwent left radical mastoidectomy and twenty years later, in 1945, commenced to suffer from vertiginous attacks.

These increased in frequency and severity, and concurrently the hearing deteriorated in both ears.

In 1948, she first attended hospital, but simple sedation and treatment along general medical lines was of no avail. In the following year therapy of a more specific nature was instituted, and included the use of nicotinic acid combined with salt deprivation and fluid limitation, a method of treatment which has been of tremendous value in most of our cases.

The patient was improved for a few months, but the attacks recurred with such severity that she was totally incapacitated, whereupon she was readmitted to hospital, and treatment with streptomycin (calcium chloride complex) was instituted. For the first fifteen days the drug was given at the rate of 2 grammes *per diem* in divided doses 6-hourly and for the remainder of the period at the rate of 2·5 grammes *per diem* until a total of 53·25 grammes had been administered. By that time caloric reactions had been abolished on the right side and very considerably reduced on the left, the side, in fact, of a radical mastoid cavity.

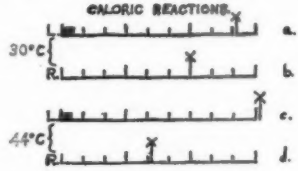

FIG. 1.—Prior to treatment with streptomycin. In tests *a* and *c* the stimulus was applied for 10 seconds only, but was followed by vomiting.

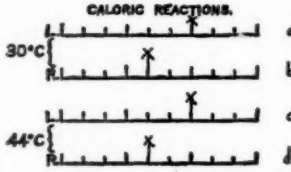

FIG. 2.—After 25 grammes of streptomycin. Tests *a* and *c* were accompanied by nausea.

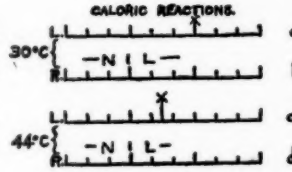

FIG. 3.—After 53·25 grammes of streptomycin. The stimulus was applied for 40 seconds in each case, but no nausea was experienced.

Audiometry was carried out at intervals and showed no obvious cochlear deterioration as a result of treatment.

Cooksey exercises were commenced early in treatment but had to be abandoned for a time, as the patient had a number of minor attacks of vertigo and was generally unwell after the second week. Physiotherapy was, however, recommenced and was continued in all for nine months. Owing to her inability, at first, to go out in the dark she did not commence work for six months after treatment, but since that time, three years ago, she has pursued her normal occupation—clerical work; has had no untoward symptoms and is extremely grateful.

SUMMARY

The two essential requirements in any particular case are: firstly that the possibility of relief with all other more conservative methods of treatment should have been thoroughly explored, and

secondly that the affliction should be bilateral. Prior to the commencement of treatment the renal function should be carefully assessed as toxic effects seem to occur more rapidly when this is impaired. The age of the patient must be taken into consideration, for the process of adjustment to an "avestibular life" is very slow in the elderly.

Throughout the period of treatment cochlear and vestibular function should be determined with regularity, and it is now my practice to have pure-tone audiometric records made at forty-eight-hour intervals; any depression of cochlear function necessitating immediate withdrawal of the drug. Lastly, the part played by the physiotherapist is of supreme importance. Remedial exercises must be applied with persistence and unflagging vigour, and the patient's morale must be continually boosted, for those who suffer from severe vertigo are often, and with reason, the most miserable of men and women.

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Mr. R. L. Flett: *The Saccus Operation in Ménière's Disease*

This operation was proposed by Portmann as far back as 1926. Its good results, however, did not seem to be maintained, and it fell into disuse until Woodman and Stirk Adams reported 10 cases in 1939. In 1938 Hallpike and Cairns showed their slides of 2 cases of Ménière's disease in which the endolymph system was tremendously dilated.

I had a severe case of vertigo who was totally deaf in the other ear. All investigations and medical treatment gave no help. He was a coal-face worker, and the coal face was 2 miles from the bottom of the pitshaft. He demanded that something should be done as he had been carried by his mates on quite a number of occasions when he had started a bout of vertigo. From the language used on these occasions, he could not risk another attack.

I thought, therefore, that the saccus operation ought to be tried. On the day after the operation his hearing had markedly improved and he could hear very satisfactorily, even through the dressings and bandages. He has maintained this condition ever since, and has no tinnitus or giddiness.

I therefore considered that instead of subjecting the severe cases of Ménière's disease to destruction of the labyrinth by injection, as I had done in the past, I should try this operation first, and if it did not succeed, I would reopen the wound and inject the semicircular canal with absolute alcohol. In fact when doing the saccus operation, I always exposed the bony external semicircular canal in readiness for injection in one week's time if it became necessary.

Since this first case I have performed this operation 73 times. This is only done in very severe cases, and I was prepared to go on to destruction, in the event of failure, in all except one other case. We carried out all the routine investigations and various types of treatment, and these cases are those which showed no response and were so severe that something had to be done.

The second case in which I did not wish to destroy the labyrinth was a woman of 40, whose right ear had become totally deaf due to a supposed labyrinthitis during diphtheria in childhood. I performed a left Portmann operation in 1941 with immediate restoration to normal. The left ear remained in this condition for three years, and then the symptoms returned. The patient stated that her hearing had been so good in the interval, that she would like the operation repeated. I admitted her and again exposed the area of the saccus. She improved just the same, but recurrence took place one year later. Operation for the third time produced no improvement. This series of procedures is not to be recommended, and seems to rank with the sudden but temporary improvement in hearing in otosclerosis from the earlier trials of the fenestration operation before Sourdille.

The saccus operation has varied from time to time. At first I used to make a large exposure behind the lateral sinus. Owing to very dilated emissary veins, the hæmorrhage was often excessive and could not always be controlled by bone wax. Sometimes packing had to be resorted to, and the rest of the operation postponed for two days. There seems to be three types of arrangement of the saccus:

(1) A small cyst with thick walls about 5 mm. in diameter. This is usually found under the small spur and is visible at operation.

(2) Instead of the small spur there is a vertical slit running down to the region of the jugular bulb, and the saccus is situated at the upper end of this slit. This is the type of case in which the dura may be opened accidentally and a flow of cerebrospinal fluid ends the operation.

(3) No bony landmarks are visible at all. The posterior surface of the temporal bone is flat, and one elevates dura from the edge of the lateral sinus for 1 to 1·5 cm. This should not be exceeded, as the internal auditory meatus on an average skull is 2 cm. from the medial edge of the lateral sinus at the level of 2 cm. down from the superior petrosal sinus. In this type no cyst may be seen at all and no opening seen in the bone.

Later on, instead of making a large opening behind the sinus, I opened the mastoid, exposing the sinus plate of bone and then exposing the sinus and working medially from that. Later still, especially in the last type of saccus, I started working in the bone posterior to the posterior semicircular canal, and either using a drill or a small gouge, and for this magnification is a great help.

Owing to the possibility of failure, I always expose the bony semicircular canal at the end of the operation. The wound is sutured with no drainage. Any case that shows no immediate improvement is reopened in one week's time and the labyrinth is destroyed.

TABLE I.—RESULTS: 74 PATIENTS

Post-operative deaths, 2	(1) Meningitis (2) Bronchopneumonia
Immediate failures, 10	Destruction of labyrinth one week later
One wrong diagnosis	Epileptic aura (this diagnosis made after six years)
19 cases with perfect result	
43 cases with some improvement	

The results can be seen in Table I. There were 74 cases in fourteen years up to December 1953.

The operation is not without danger as there were two post-operative deaths, one from meningitis —streptococcal in type, in a case that had to be opened twice owing to hæmorrhage the first time. The second case died of bronchopneumonia five days after the operation. There were 10 immediate failures, and these required destruction of the labyrinth one week later. There was one which I may term a wrong diagnosis; she was not improved at all, and it took us and the neurological physicians six years to decide that this was due to an epileptic aura. There were 19 cases with a perfect result, that is the hearing showing only 10 decibels loss over the speech range with slightly increased higher-tone loss. The remaining 43 cases showed some improvement. I shall now analyse these 43 cases in Table II.

TABLE II.—43 CASES WITH SOME IMPROVEMENT

Giddiness				
Disappeared	Improved	No improvement		
23	13	5		
Tinnitus				
None	Slight or used to it	Colds cause buzzing	Bad	
14	8	2	10	
Deafness				
Normal hearing	No improvement or worse			
7	33	50–70 decibels loss, and of these 9 have hearing aids		

With regard to giddiness: It had disappeared in 23, improved in 13, and showed no improvement in 5, and by rights these 5 cases should really have their labyrinths destroyed. The tinnitus had disappeared in 14, 8 cases complained of slight tinnitus or had become used to it, colds cause buzzing in 2, and 10 complained of severe tinnitus, as, for example, like a bomb whistling down; heavy work makes palpitation go to the right ear, especially moving the right arm. I also saw 2 cases where the tinnitus was almost unbearable. I have had some of these show delay in improvement in the noises, or noises may come on again in three months' time and can later, for no apparent reason, disappear.

With regard to hearing. 7 of these cases show hearing loss up to 10 decibels over the speech range, and I have put these down as normal. The remaining 33 show no improvement or have become worse, that is 50–70 decibels loss, and of these 9 have hearing aids.

I shall further discuss the giddiness in those cases who have improved:

(1) Complained of slight giddiness in 1950, ten years after the operation, but he used to have severe giddiness with vomiting and diarrhœa and has not had to stay off work.

(2) Had two attacks in ten years, was off work once for five weeks and another time for two weeks.

(3) Complained of slight giddiness with colds, but could carry on his work.

(4) Becomes slightly lightheaded with noises at times.

(5) Eight years after the operation had one attack of giddiness. He was operated on at the age of 15.

(6) Is aged 71 and complains of slight giddiness when doing too much work, especially with the arm upward.

(7) Had one short attack eight years later but none since.

(8) Has been off work one month, eight years after the operation, but the attack was much less severe.

(9) Complained of slight giddiness on turning over in bed or stooping suddenly.

(10) Is a miner who complains of slight giddiness on walking in the dark, especially in the coal pit.

(11) Three years after the operation complained of slight giddiness.

(12 and 13) Complained of a feeling of general swimminess with no bouts of giddiness.

In these cases there was sometimes a delay in improvement up to one year, and indeed 2 of them during this time were put on the waiting list for destruction of the labyrinth, and later reported saying that they did not wish the operation to be performed as they were much better.

I reported a series of these in Toronto at the Triological Congress in 1952 (Flett, 1952). This was a ten-year review from 1939–1949, and the results were not highly encouraging. Also Altmann at the Presbyterian Hospital in 1945 had reported 11 cases with only temporary result. To those cases I have now added 13 more. The only extenuating circumstances I can plead are these:

(1) It offers a 25% possibility of retaining the hearing and stopping the tinnitus and giddiness.

(2) It enables 61% of them to continue at work with no giddiness, or only swimminess, but with gradual loss of hearing.

(3) It fails in 14%.

From these results it can be seen that a small proportion can retain their immediate post-operative condition. I consider it is worth while to continue this saccus operation as a preliminary to doing the destructive operation, and that sometimes need for destructive operation does not arise.

Two years ago I stated that I had not destroyed a labyrinth since 1947. In the last two years I have done this twice for failure of the saccus operation. In one I removed the membranous canal. He had 30 decibels loss before the operation. Afterwards it was still 30 decibels loss and two months later went down to 60 decibels. Unfortunately, he had since had another giddy attack, but not as violent as his previous ones.

In the other case I removed the canal, and in order to promote further destruction, injected the labyrinth with absolute alcohol. In the anæsthetic room, she told me she had just started a giddy attack half an hour before, she could not open her eyes, the nystagmus was severe, and she said, "I shall be glad to have the anæsthetic to stop this attack". I had never operated on a case in the acute condition and I thought this would be a good opportunity to see the membranous canal. It was an absolute cast of the bony canal, a wide sausage-shaped tube. I divided it at both ends with a sharp needle and removed it by forceps. On section, however, the only thing remaining was the ampullary end, and everything else was distorted. I compared it with a normal semicircular canal, as I wondered whether there might be any difference in cell spacing or nuclear spacing. If, however, anyone is used to preparing these small specimens, it would be interesting to keep these patients on a waiting list until their acute attack, and admit them for immediate removal of the membranous labyrinth, and actually see and photograph in the living that pathological appearance that Hallpike described. As regards the specimen, the unsupported membranous canal, I should like advice as to the best means of securing a respectable microscopical appearance.

To return to the saccus endolymphaticus, owing to difficulty in finding it, I am going to use the frozen section technique in those cases when it cannot easily be found. Lindsay (1951) in Chicago has done a tremendous amount of research in cats conditioned to auditory stimuli, and has found that destruction of the saccus or aqueduct, has produced no change in the hearing, behaviour or histological appearance of the labyrinth. They were normal cats and I should like to suggest that a trial be made to induce Ménière's disease by either a highly fluid diet, or a high salt intake and then, if successful, to try the saccus operation.

Lempert (1952) has shown specimens of the membranous canal preserved and sectioned in celloidin, and has noted vesiculation of the epithelium. He has put forward a theory on this, that the attack is due to rupture of the vesicles, and the severity of the attack depends on the number ruptured. It could also be argued that the vesicles may obstruct the aqueduct. However, my slide does not show these vesicles, which, of course, may have ruptured in the attack.

In future cases I intend to expose the saccus and also to expose the external semicircular membranous canal or posterior semicircular membranous canal. If they are distended, I shall note whether there is any change in the condition after opening the saccus.

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Dr. **Oliver Gray** showed a few lantern slides illustrating the anatomy of the structures which had come under discussion, two of which are included on this page. Without claiming any originality, he emphasized the value of speaking of the semicircular *ducts* lying within the semicircular *canals*. This improvement on the old terminology was in every way desirable, and, further, took into account the fact that the semicircular *ducts* of fishes, become, in amphibians, reptiles, birds and mammals, surrounded by the semicircular *canals*.

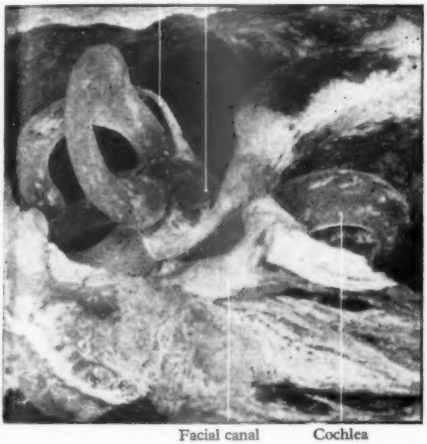

FIG. 1.—Perspex preparation of the right human labyrinth viewed from above. Note the aqueduct of the vestibule and other related structures.

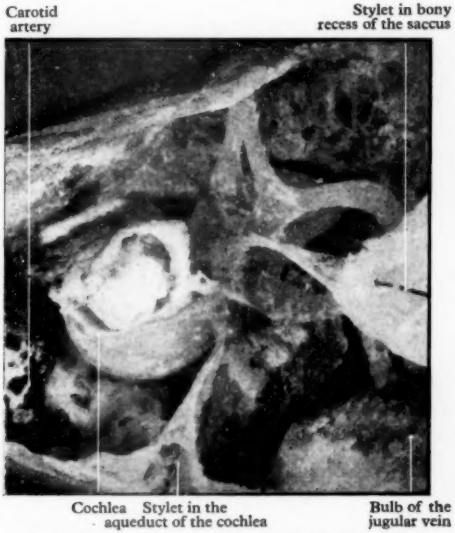

FIG. 2.—Perspex preparation of the right human labyrinth looking outwards.

Mr. E. D. D. Davis said from his own experience true Ménière's syndrome, i.e. true aural vertigo, was apparently difficult to diagnose. He had collected 100 cases of vertigo and only 19 out of the 100 were true Ménière's disease or syndrome. The characters of a true aural vertigo were a paroxysmal rotatory giddiness similar to that produced by syringing the ear with too hot or too cold lotion. The tinnitus was marked before or during an attack. The deafness was unilateral and a condition of the ear known to produce vertigo was present. Labyrinthine nystagmus occurred only during the attack. Diplacusis, or a distorted hearing, might be present. Loud noises were almost painful and might bring on an attack. The vertigo of thyrotoxicosis, *petit mal* or postural giddiness were not Ménière's syndrome. Alcohol aggravated or might produce an attack of vertigo in a susceptible patient. All cases of vertigo were not aural or Ménière's disease. He would like to ask Mr. Cawthorne how he decided which ear caused the vertigo in a case where both ears were affected.

Mr. C. A. Hutchinson said there was one point he would like to ask Mr. Cawthorne: Whereas Dr. Hewlett had referred to Shambaugh's statement that there was an association between otosclerosis and labyrinthine hydrops, he had noticed that Shambaugh went further than this and suggested (*Acta Otolaryng., Stockh.*, 40, 215) that "The fenestration operation definitely predisposes an ear to the subsequent development of a hydrops (10%)". Was Mr. Cawthorne of the opinion that, in this country at all events, there was any evidence to support this statement?

Mr. I. B. Thorburn said in his discussion of the pathology of Ménière's disease Mr. Cawthorne had, perhaps, concentrated unduly on hydrops of the labyrinth. He suggested that in the over-50 group of patients vertigo and perceptive deafness was often caused by a vascular lesion of the labyrinth associated with generalized arteriosclerosis.

He thought further that the discussion on methods of destroying the labyrinth was unnecessarily complicated. Having made an opening into the lateral semicircular canal, the simplest and most effective way to destroy the labyrinth was to apply the sucker to the opening.

Mr. S. W. G. Hargrove asked if a geographical survey had been made of the incidence of Ménière's disease in this country. He worked in a rural area where people were well fed. He looked at his own statistics before coming to the meeting and found that in the last year he had seen only 10 cases of true Ménière's disease in his outpatients and in nine years he had carried out one labyrinthectomy. Had Mr. Cawthorne any experience in sectioning of the chorda tympanic nerve such as was described by Rosen, S., 1954, *Lancet*, i, 133?

Mr. P. E. Roland spoke of the effect of stellate block. Mr. Cawthorne had explained that it did not cause vasodilatation of the vessels but he had found that it had been effective in many cases. In 2 out of 3 cases of an acute attack of Ménière's disease he was able to give the patient great relief within a few minutes and in a number of cases he had found that one injection had given prolonged relief.

Mr. Terence Cawthorne, in reply to Mr. E. D. D. Davis, said that it was not as a rule difficult to diagnose Ménière's disease. In order to arrive at a precise diagnosis, however, it was important to carry out a full otological examination including the tests not only of auditory but also of vestibular function. Mr. Davis had also mentioned the question of which ear was in the active phase in bilateral cases. Such patients could indeed be a problem but he would like to emphasize again that this was about the only time in otology when tinnitus was really useful, because it would often indicate which was the affected ear. Time and time again he had noticed in bilateral cases that tinnitus or a feeling of fullness in the ear indicated which ear was in the active phase.

Mr. Hutchinson had asked about the possibility of Ménière's disease following fenestration. Shambaugh in his monograph went so far as to say that almost 10% of his cases developed hydrops following fenestration. He had no accurate figures to show what proportion of cases followed fenestration but he would think it was something like 2%.

Mr. Thorburn had mentioned the possibility of a vascular lesion particularly in elderly cases. The blood pressure had been noted in a series of cases of Ménière's disease and was found to be rarely more than one would expect from the population at risk. Mr. Thorburn mentioned removing the labyrinth with a suction tip. This was only too easy as some had found when performing other forms of operation on the labyrinth. He felt that it was best to remove the membranous canal with fine watchmakers' forceps. In this way one had proof that the operation had been properly done. In no case of Ménière's disease in which the membranous canal had been removed or even cut across had there remained any trace of cochlear or vestibular function. He had known of cases in which the labyrinth had to be destroyed for some disorder other than hydrops, and he believed that in such cases it was wise to inject a few millimetres of alcohol as well.

Mr. Hargrove had mentioned a geographical study. He (the speaker) could say that more than half his patients came from outside the London area.

There did not seem to be any evidence at all that the chorda tympani had any other function than that of taste. He had had the opportunity of cutting the chorda tympani accidentally in cases of otosclerosis when carrying out a fenestration operation and the giddiness after the operation was just the same. He had also found that touching the chorda tympani at a fenestration or at a radical mastoid dressing might give rise to a sensation of metallic taste but not of vertigo or tinnitus. He felt a little more proof was needed that the chorda tympani had functions other than that of taste before patients were submitted to what could only be described as an extremely hypothetical procedure.

The value of stellate ganglion injections in cases of Ménière's disease, particularly during the acute phase of the attack, had been mentioned, but unfortunately he had not found it of any great value. He had been able to inject the ganglion in 2 cases of Ménière's disease during an attack but it did not seem to have any influence. However, in all fairness he should say about stellate injections that every now and again patients did say that the tinnitus had gone, perhaps only for a few minutes or a few hours, so that something must be happening within the labyrinth but what it was he did not know.

Section of Radiology

President—J. BLAIR HARTLEY, M.D., F.F.R., D.M.R.E.

[*February* 19, 1954]

Planning a Clinical Trial of Radiotherapy for Intracranial Gliomata

By JOHN PENMAN, M.R.C.P.

SCIENTIFIC method and the treatment of a sick human being always form an uneasy partnership, and never more uneasy than when the treatment is radiotherapy of an intracranial glioma.

Let us imagine two cases, neither of them improbable. First, here is a farm labourer aged 65 years, uneducated, inarticulate, and uncomplaining by nature, who begins to have headaches and lack energy. After what his wife, when giving the history later, calls a decent while, he goes to his general practitioner, who gives him aspirin and a sedative. After a further decent while, his wife becomes worried by his vomiting and apathy, and so he is admitted to a nearby hospital, where his drowsiness soon causes alarm. His optic discs are then examined, papilloedema is found, and he is transferred post-haste to a neurosurgical unit, arriving semi-comatose. Ventriculography suggests that he has a right frontal tumour, and through a burr-hole in that region some brain tissue is obtained for biopsy. The pathologist reports that it has the appearance of an astrocytoma, grade 3. The plan is to give radiotherapy, but twelve hours after biopsy the patient dies. Permission for necropsy is refused.

Secondly, here is a highly educated woman aged 22 years. One week-end (and when giving the history she can state which week-end it was) she begins to suffer from pains in the head, nausea and impaired mental concentration. Four weeks later she goes to her general practitioner, who at once makes a provisional diagnosis of a brain tumour. A week after that, she is admitted direct to a neurosurgical unit, still in good general condition and quite alert, but with some blurring of vision and early papilloedema. Ventriculography shows the aqueduct kinked and the fourth ventricle displaced backwards. Biopsy is out of the question, but clinically and radiologically this case strongly resembles others in which necropsy has proved the presence of a pontine glioma. First ventriculo-cisternostomy is carried out, and then the patient receives a full course of radiotherapy, towards the end of which her symptoms improve and her optic discs begin to subside. Twelve months after operation she is seen at follow-up; she still has some impairment of visual acuity and is aware of it, but otherwise feels well, and is at her former work. Her optic discs are pale but she shows no other abnormality. Eighteen months after operation she fails to answer a follow-up letter, and proves to have moved house, leaving no new address.

How well the second patient has done with radiotherapy, and how poorly the first did without! Surely, then, it must be a highly beneficial treatment. Childish though such a way of reasoning may appear when presented in this extreme form, nevertheless we are all in danger of falling into it. It is interesting to consider how much we need to know, and do not know, about our two hypothetical patients. In the case of the woman, did her sex or her youth contribute anything towards the good result? How long had the man been ill before operation? How much did ventriculocisternostomy benefit the woman? In which site is a given glioma more responsive to X-rays, the right frontal lobe or the pons? If necropsy had been allowed in the man's case, would his tumour as a whole have turned out to be histologically similar to the biopsy specimen? How has the woman been getting on since we lost sight of her? Did she have a glioma at all? If we could have proved that she had one, would it have belonged to the same histological group as the man's glioma? Suppose she had an astrocytoma of the lowest grade of malignancy; which, in itself, would be more responsive to X-rays: her glioma or the man's? Lastly, when we say "responsive to X-rays", do we mean treatable in the short run or curable in the long run?

Other pairs of patients, as different as those two but in other ways, are equally easy to imagine; and one cannot evaluate any treatment until such differences have been eliminated, or at least reduced. The present clinical trial is an attempt to reduce them.

As Professor Bradford Hill has taught me, the first step must be to ask oneself an unambiguous question, which in this case is as follows. Suppose a patient to have an intracranial glioma for which he undergoes operation; what difference will it make to the length of his life after operation if he is irradiated as well? The plan which I shall now describe is the result of discussion between Mr. Wylie McKissock, Mr. Valentine Logue, Professor Theodore Crawford, Dr. William Blackwood, Professor D. W. Smithers and myself; it comprises nine points:

(1) *Uniformity of surgical methods.*—All the material is provided by Mr. McKissock and Mr. Logue. No two surgeons' methods are identical, but these two know each other's methods very well, and for the present purpose are keeping their treatments as similar as possible.

(2) *Strictness and uniformity of histological diagnosis.*—In every case in which brain tissue has been obtained for biopsy, one and the same microscope slide is passed round between three pathologists who give their independent opinions on it. Two of the three are always Dr. William Blackwood and Dr. J. W. Whittick, and the third is either Professor Crawford, Dr. W. H. McMenemey or Dr. Martin Bodian. Five kinds of histological diagnosis are acceptable for the clinical trial: astrocytoma (or astroblastoma) of grades 1, 2, 3 and 4 in Kernohan's classification, and oligodendroglioma (or oligodendroblastoma). Grades 1 and 2 of astrocytoma are regarded as a single pathological group, grades 3 and 4 (corresponding to glioblastoma in the older terminology) form another single group, and oligodendroglioma forms a third group.

Table I shows in detail how the histological reports are sorted into five pathological groups, to which there is added a sixth, for presumed gliomata without biopsy.

TABLE I.—RESULTS OF BIOPSY

Opinion of	
All three pathologists: "astrocytoma, grade 3" or "astrocytoma, grade 4" (N.B. astroblastomata are counted as astrocytomata)	Glioblastoma (G)
Two pathologists: as above. Third pathologist: any other kind of glioma	Glioblastoma (G)
All three pathologists: "astrocytoma, grade 1" or "astrocytoma, grade 2"	Astrocytoma (A)
Two pathologists: as above. Third pathologist: any other kind of glioma	Astrocytoma (A)
All three pathologists: "oligodendroglioma" or "oligodendroblastoma"	Oligodendroglioma (O)
Two pathologists: as above. Third pathologist: any other kind of glioma	Oligodendroglioma (O)
One pathologist: G. Another: A. Third: O	Controversial (C)
One pathologist: G, A or O. Another: also G, A or O. Third: not a glioma (e.g. normal brain tissue, or a metastasis)	Questionable (Q)
No biopsy	Deep unverified (D)

(3) *Exclusion of unsuitable forms of glioma.*—We have excluded medulloblastomata, because the evidence for their being radiosensitive is comparatively good; and astrocytomata limited to one cerebellar hemisphere, because the surgeon can completely excise them, leaving no tumour tissue to need irradiation. Ependymomata are believed by some people to resemble medulloblastomata in being especially radiosensitive, and are in any case rare, and so we have excluded them also.

(4) *A moderately simple classification of cases.*—When it comes to classifying, zeal has to be restrained because of time and space. Table II is a list of prognostic features, each perfectly reasonable in itself; if due regard were paid to all of them, the number of ultimate subdivisions would be over a thousand million, or about half the present population of the globe.

TABLE II.—FEATURES INFLUENCING PROGNOSIS

	Factor	Product
Sex	2	2
Age within same quinquennium	16	32
Length of illness before operation: say (1) 0-3 months, (2) 4-6 months, or (3) 7+ months	3	96
Presence or absence of headache	2	192
papilloedema	2	384
vomiting	2	768
epilepsy	2	1,536
hemiparesis	2	3,072
Level of consciousness immediately before ventriculography: (1) alert, (2) drowsy but responsive to spoken word, (3) responsive not to spoken word but to a standard painful stimulus, or (4) responsive not even to the standard painful stimulus	4	12,288
Pressure of ventricular C.S.F.: (1) normal, (2) moderately high, or (3) very high	3	36,864
Site of tumour	20	737,280
Size of tumour: (1) large, (2) medium, or (3) small	3	2,211,840
Degrees of surgery :		
Ventriculogram or not	2	4,423,680
Tapping of cyst or not	2	8,847,360
Burr-hole biopsy or not	2	17,694,720
(1) no removal (apart from burr-hole biopsy), (2) partial removal, or (3) total excision	3	53,084,160
Ventriculocisternostomy or not	2	106,168,320
Histology: astrocytoma, grade 1, 2, 3 or 4; or oligodendroglioma, grade 1, 2, 3 or 4; or controversial; or questionable; or deep unverified	11	1,167,851,520

Table III shows the actual classification adopted for the present enquiry. One could hardly do less than divide patients, as here, by sex, into two age groups, by two degrees of surgery and into four main pathological groups; but, as we have seen, two more subsidiary groups are needed, and the

TABLE III.—ACTUAL CLASSIFICATION OF CASES

(1) *With biopsy*

	Factor	Product
Male (M) or female (F)	2	2
Age at operation:		
0-39 years (J) or 40+ years (S)	2	4
Extent of operation:		
Burr-hole biopsy (L) or any larger operation (E)	2	8
Histology:		
Glioblastoma (G), Astrocytoma (A), Oligodendroglioma (O), Controversial (C) or Questionable (Q)	5	40

(2) *Without biopsy*

Deep unverified (D)		
M or F	2	2
J or S	2	4
With biopsy		40
Without biopsy		4
Total		44

outcome is 44 ultimate subdivisions. That is not quite so bad as it sounds. Table IV shows that after the first 12 months of the enquiry, 16 of the possible 44 subdivisions were still empty, and some subdivisions already contained a substantial number of cases. At the present rate, for example, the subdivision M S L G, at the end of another two years, will probably contain enough cases to yield statistically reliable conclusions by itself.

TABLE IV.—NUMBERS IN ULTIMATE SUBDIVISIONS AT END OF FIRST 12 MONTHS

M S L G	32	M J D	7
F S L G	16	F J D	4
M S E G	12	F S D	4
M S E A	10	M S D	2
F S E G	7		—
M J E A	5		17
F J E G	5		—
F S E A	5	F S L Q	3
M J E G	3	M S L Q	2
M J L G	3	F S E Q	2
M S E O	3	M J E Q	1
M S L A	3	F J E Q	1
F J L G	3		—
F S L A	3		9
M J L A	2		—
F J E C	2		
F S E O	2		118
M S L O	1		17
F S L O	1		9
	—		—
	118		144

(5) *Uniformity of starting point for measurement of survival.*—Each patient's survival is measured from the day of his principal operation; that is ventriculography, if that was the most that was done in the way of surgery; or burr-hole biopsy, if that was the most; or craniotomy, if that also was done.

(6) *A fixed minimum period of survival for inclusion in the series.*—If one were to include every patient who had lived, say, 4 weeks after operation, the radiotherapist would justly protest that many so-called irradiated patients had died after only a negligible total dose of X-rays. On the other hand, if one included only those who had lived, say, 12 or 16 weeks after operation, in order that every single irradiated patient in the series should be quite completely irradiated, then the total number of cases would be needlessly reduced. In this clinical trial a minimum of 56 days was agreed on as a fair compromise by surgeons, pathologists and radiotherapists. If, as a result of exceptional delays, a patient dies more than 56 days after operation, and yet without his full dose of X-rays, that is considered to be one of the inevitable imperfections of the system of radiotherapy and he is still regarded as an irradiated patient. Full records are kept of the patients who die in less than 56 days, so that it will be possible to alter the minimum period retrospectively if we wish.

(7) *A simple method of determining whether a given patient shall be irradiated or not.*—Within each ultimate subdivision, the chronologically first patient is intended for irradiation, the second is unirradiated and so on alternately. I say "intended for irradiation" because of course any patient may die too soon for it.

(8) *Comparative uniformity of methods of radiotherapy.*—All irradiation is carried out at the Royal Cancer Hospital, Chelsea, by Dr. Simon Kramer on behalf of Professor Smithers. Beyond that, no uniformity is possible; one cannot standardize the total dose of X-rays, nor the number of separate doses, nor even the type of apparatus used. Like the surgeon, the radiotherapist must have a free hand in treating each individual according to his judgment; but we have at least secured that similar cases will be treated by very similar methods.

(9) *Uniformity of follow-up.*—The dates aimed at for follow-up are 56 days after operation, 112 days after operation, and so on every 56 days. Patients are never seen before the correct date, and usually not more than a week or two after it. Whenever it is possible, the irradiated and the unirradiated are interviewed and examined on the same day and by the same two observers together, namely by Dr. Simon Kramer and myself. Points to which we pay particular attention are whether the patient is at his former work and getting his former wages, whether pre-operative symptoms and signs persist, whether the scalp over the burr-holes is sunken or bulging, and the visual acuity.

Some patients, needless to say, live in remote parts of the British Isles and are too ill to be brought to London; and one, who is very well, has gone to live in Australia. So far, however, no patient has been entirely lost sight of, and no death has occurred without our ascertaining its date fairly accurately. One unirradiated patient, despite a request to the contrary, has been given radiotherapy elsewhere and has had to be rejected.

I wish to thank all the experts whom I have already named, and also those physicians who have kindly allowed their patients to be included in the trial. I owe a special debt of gratitude to Dr. Marion Smith, my collaborator in an earlier clinical study of 300 gliomata treated by Mr. McKissock. That study showed us the lack of evidence about the effects of X-rays on gliomata, and gave me some useful experience of the problems which still face us. The present enquiry is being aided by a generous grant from the Medical Research Council.

Finally, I trust it will be understood that at this stage I can say nothing whatever about results.

Section of Surgery

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*April* 7, 1954]

THE SURGERY OF CONJOINED TWINS

Professor Ian Aird:

The Conjoined Twins of Kano

Professor Ian Aird showed a 16 mm. colour film with sound track made for the Postgraduate Medical School of London at Hammersmith Hospital by Stanley Schofield Productions Ltd. The details of the operation have been fully reported in the *British Medical Journal* (1954) i, 831 (April 10). Four black and white illustrations prepared from the film by Kodak Ltd. follow:

FIG. 1.—Separate anæsthetization of the twins.

FIG. 4.—Completion of the operation.

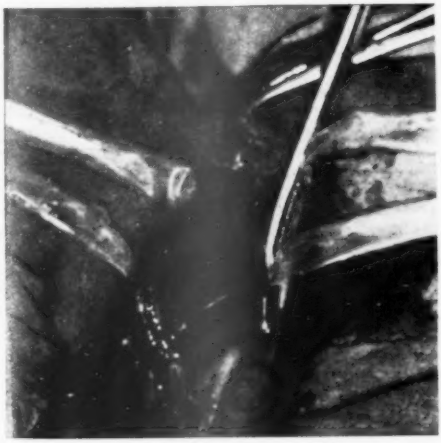

FIG. 2.—Exposure of the liver bridge with tourniquets in place.

FIG. 3.—Division of the liver bridge approaching completion.

Professor W. J. Hamilton (Charing Cross Hospital Medical School):

A Note on the Embryology of Twinning

Twins may be monozygotic (identical or like) or dizygotic (fraternal or unlike). In the human subject twins occur in about one in ninety births and about one-quarter of all human twins are monozygotic. It is only monozygotic twins that are under discussion in the present communication.

In embryology an idea fundamental to the study of differentiation is the concept of determination. By this term is meant the possible fates of different cells of the developing egg (blastula, blastoderm or blastocyst). Before this restriction occurs the cell or cells are totipotent or plastic. Before cleavage

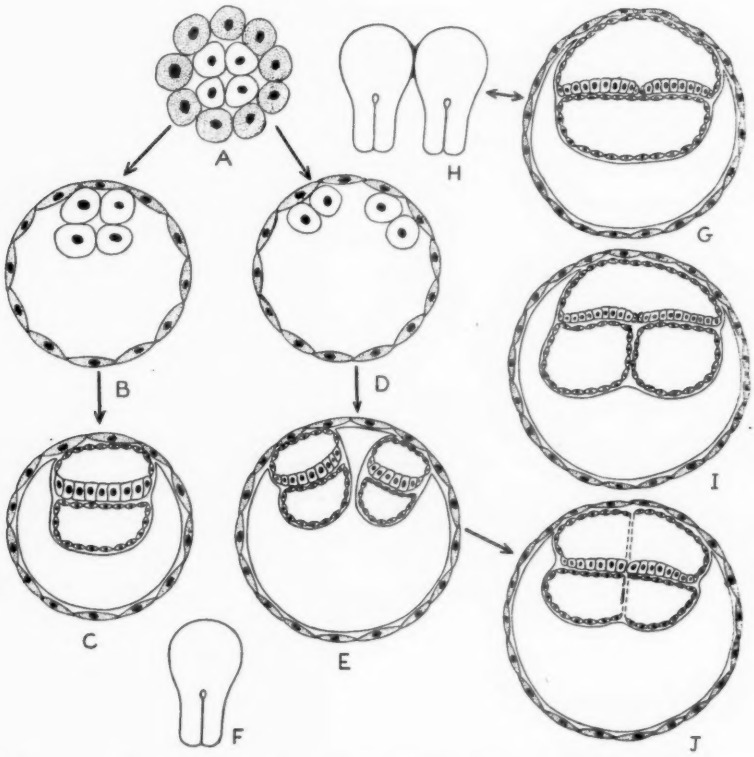

FIG. 1.—A, Morula. B, Normal blastocyst with a single inner cell mass of which four blastomeres are shown. C, Blastocyst in which the inner cell mass has differentiated to form the embryonic disc. D, Blastocyst with two inner cell masses each of which is indicated by two blastomeres. E, Blastocyst with two separate embryonic discs. F, Dorsal view of inner cell mass at the primitive streak stage. G, Two embryonic discs within a single inner cell mass. H, Dorsal view of fused embryonic discs at the primitive streak stage. I, Two embryonic discs with separate yolk sacs derived from a single inner cell mass. J, Fused embryonic discs—possibly derived from E.

Trophoblastic cells are shown in stipple.

in some eggs, or during cleavage in most eggs, the totipotency of the egg is reduced so that material is segregated into areas which have restricted organ-forming potencies.

The early experimental work of Roux (1888) on the amphibian egg at the stage of two blastomeres showed that if one of the blastomeres was destroyed then only half an embryo developed. Subsequently Driesch (1891), working with the sea urchin egg, and Wilson (1893), with the egg of amphioxus, showed that complete embryos could be obtained from a single blastomere of the two-cell or four-cell stages. These studies initiated the experimental approach to the study of monozygotic or identical twins.

Since these investigations were carried out numerous studies have been made on developing eggs

of many different species. In order that twins may be produced in a cleaving egg or blastoderm certain conditions in each of two parts are essential:

(1) A sufficiency of protoplasm must be present and this must contain each of the different materials required in order that all the organs can eventually be produced.

(2) In the protoplasm an organizing centre must be present in order to integrate the developmental stages and regulate the arrangement of the materials and compensate for loss.

In the teleost fishes monozygotic twins occasionally occur during normal development. Usually in the late blastula only one organizing centre becomes dominant and suppresses the tendency to totipotency in the remainder of the blastoderm so that a single embryo is formed.

If normal development is arrested for a time by some adverse influence, e.g. experimentally, either by lowering of the temperature or through lack of oxygen, then two centres of organization may make their appearance and twins are produced. If the organizing centres are close to each other the embryos may be fused laterally. If the blastoderm is completely divided experimentally separated twins arise. If the division is incomplete conjoined twins result.

In the avian blastoderm, as has been shown by Wolff and Lutz (1947), it is possible to produce twins by dividing the early blastoderm (at the early primitive streak stage) into right and left halves or into an anterior and a posterior half. Here again if the division is incomplete conjoined embryos are formed.

In mammals the early development of the egg is more complex owing to the early segregation of material into trophoblast and inner cell mass (Fig. 1, A). It is known that the blastomeres at the two-cell stage are similar in appearance and it is assumed that each cell is capable of giving rise to a complete embryo. It is possible that in mammals twins could arise if the blastomeres were separated from each other (*see* Nicholas and Hall, 1942). There is, however, convincing evidence that separation of material does not occur in mammals until the blastocyst stage.

If the inner cell mass proceeds to develop in the usual way it gives rise to one embryo with its related yolk sac and amnion (Fig. 1, B and C). If the inner cell mass becomes divided more or less equally into two masses two embryos are formed with the related yolk sacs and amnions (Fig. 1, D and E). A number of such specimens at an early stage of development has been found in mammals and in man. If the separation is incomplete conjoined twins are formed. If the separation is grossly unequal or if one component is better placed so that it can monopolize more of the placental blood then the less favourably situated mass may become a parasite on or within the other twin. There is a further possibility that two organizing centres may occur in a single formative area and give rise to twins (Fig. 1, G and I). If separation is incomplete or if the organizing centres overlap in their spheres of influence then various forms of Siamese twins will be produced.

In one mammalian group (*dasypodine armadillos*) the fertilized egg normally gives rise to four embryos (Patterson, 1913) which are always of the same sex and all of which have a common chorion and amnion. A blastocyst with an inner cell mass is formed. This mass then divides into two and eventually into four masses, each of which gives rise to an embryo.

The blastocyst in the armadillo exhibits what is known as delayed implantation. The blastocyst normally lies free in the uterus for about three weeks before implanting. During this period development is slowed down (Patterson failed to find mitotic figures in blastocysts during this period) and this may allow the development of separate organizing centres in the egg. There is no evidence, however, that delayed implantation occurs in twinning in the human subject.

Why the inner cell mass in mammals, including man, should occasionally separate into two masses is unknown.

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Dr. J. P. S. Wijthoff (Oenkerk, Holland):

The Conjoined Twins of Friesland

Surgical aspects.—It is now clear to me beyond doubt that not only the surgical technique is of importance for the operation to separate conjoined twins but that most urgent of all is the most elaborate pre-operative investigation of such twins, with regard to all sort of varieties one can encounter in outwardly identical twins.

The Hastings case (*Brit. med. J.*, 1954, i, 833), the Kano twins and our pair are probably a series of decreasing of the conjoined area.

Our pair of twins, girls, had a combined birth weight of 6·5 kg. and a length of 50 and 49 cm.; the height of the anastomosis was about 7 to 10 cm. (depending on the distance between or the traction exercised on them) and its circumference was about 25 cm. The communication extended from the xiphoid bone to the umbilicus and was easily movable.

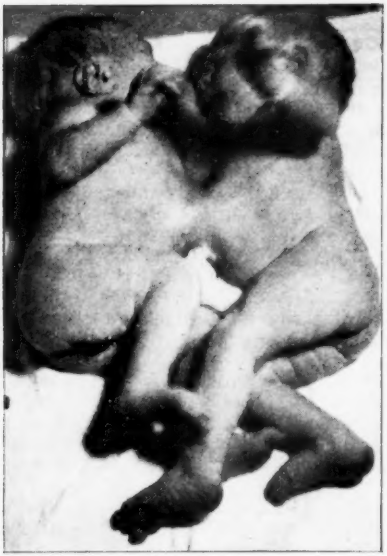

FIG. 1.

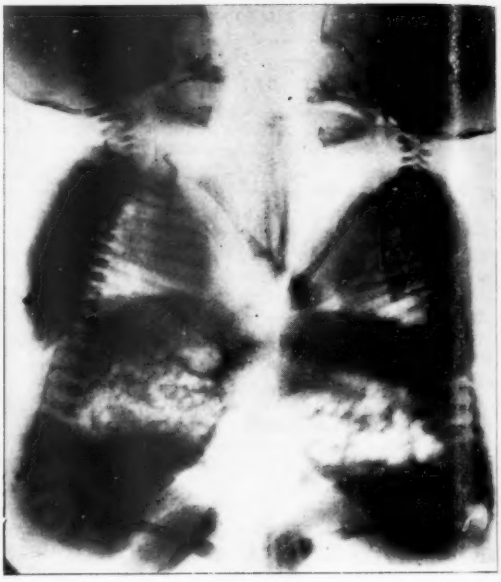

FIG. 2.

The twins are now five months old and one can feel a cartilaginous connexion between the two sterna. Beneath this one cannot now feel any organs which give resistance to the palpating fingers; below there is a small umbilical hernia. The breasts are in a normal position. There is no open communication between the stomachs, or the small and large intestines. The X-rays of gall-bladders and uropoietic organs, and the studies of the bloodmixing will be done during the coming month, as well as the Thorn test and other possible hormone experiments. Injection of carmine red in one of the twins gave only a little blue colouring of the urine of the other girl but on the other hand caused some collapse of the first child, so that we postponed further tests to a later date.

Dr. Josephine M. Lord (Pædiatric Unit, St. Mary's Hospital, London):

Intra-abdominal Fœtus In Fœtu—2 *cases*[1]

After this fascinating account of the separation of externally attached twins, some mention of included twins may be of interest.

Case I.—In July 1950 a 7 weeks' old boy came under my care at the County Hospital, Hereford, on account of progressive enlargement of the abdomen.

Family history.—The mother's great-grandmother gave birth to twins.

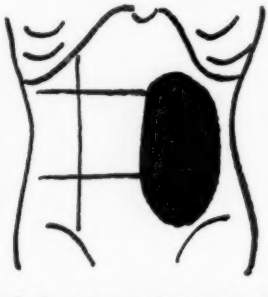

FIG. 1 (*Case I*).—Diagram showing position of the tumour in a boy aged 7 weeks. Smooth, hard mass, movable from side to side. Not emerging from thorax or pelvis. No evidence of free fluid.

History.—The mother's pregnancy was uncomplicated and the child was delivered normally four weeks before term, his birth-weight being 7½ lb. For the first week of life he was cyanosed but during the second

[1] Extract from London University M.D. Thesis, 1954.

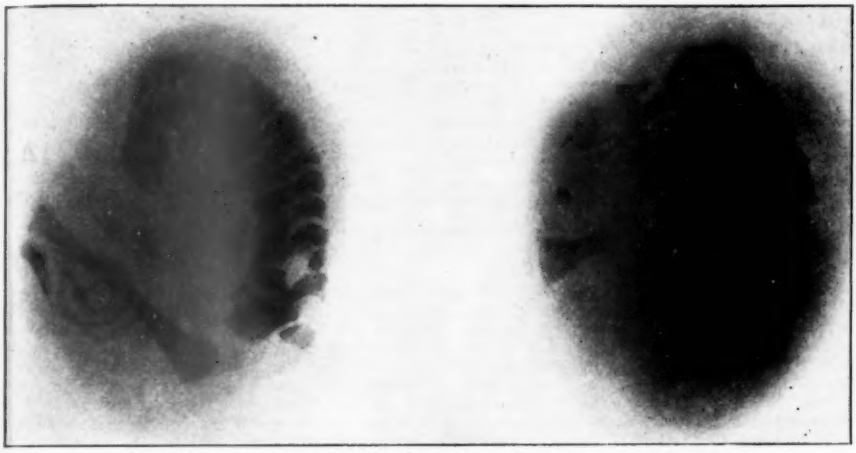

FIG. 2 (*Case I*).—X-ray of surgical specimen from a boy aged 7 weeks.

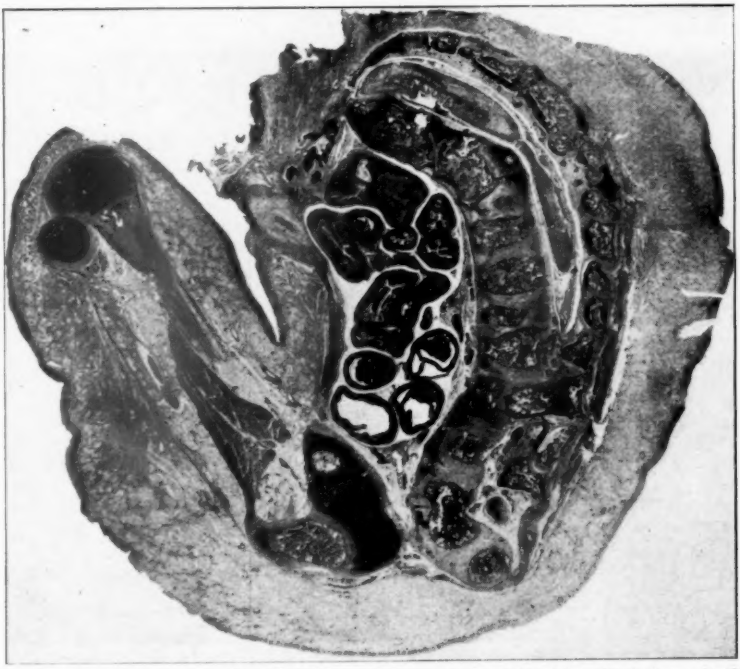

FIG. 3 (*Case I*).—Complete cross section of specimen in an approximately mid-sagittal plane. In the posterior region (to the right in the figure) lies the vertebral column, cut slightly obliquely so that the canal, containing the spinal cord, is only included superiorly. In the pre-vertebral region, at approximately the mid-point, is seen the minute adrenal gland forming an inverted pear-shaped structure. In the cavity anteriorly lie coils of intestine cut in cross section. Projecting anteriorly from the inferior pole of the specimen is a "limb" appendage, the proximal and distal portions of the included bony shaft being present in the plane of section, whilst bundles of voluntary muscle occupy the mid-shaft region. The whole specimen is clothed in skin, with a thick subcutaneous layer of adipose tissue. H. & E. preparation. Natural size. By courtesy of Dr. L. L. R. White and Mr. Derek Martin.

week his colour became normal but the mother noticed that his abdomen was swelling until at the age of weeks it "seemed as if it would burst".

On examination.—He was a thin infant, weighing 9 lb. 1 oz. His abdomen was distended by a sausage-shaped tumour extending from the left costal margin to the brim of the pelvis (Fig. 1). Both testicles were descended. The tumour was thought to be a teratoma. However, the straight X-ray of the baby's abdomen showed within the tumour the bones of an imperfect vertebrate skeleton.

The case was therefore referred to the obstetricians, Mr. P. Brown and Mr. P. Devlin. They successfully removed an encapsulated tumour which presented through the lesser sac, was adherent at its base to the duodenojejunal flexure and was attached to the posterior abdominal wall by a pedicle in the neighbourhood of the lower pole of the left kidney.

The wound healed by first intention, the child was discharged home thirteen days after operation and is now well at the age of 3½ years.

The tumour is ovoid with its pedicle inserted into a "ventral" hilar depression. There are three apparent limb buds bearing digits equipped with nails. A dark greenish thin-walled sac is attached to the superior part of the ventral surface, and a tuft of hair lies just above this sac.

The X-ray of the specimen (Fig. 2) reveals a vertebral column showing cranio-caudal differentiation and related appropriately to ribs and a pelvic girdle. One scapula is clearly seen and there is one femur related distally to bones resembling the proximal portions of a tibia and fibula.

The pathology was studied by Dr. L. L. R. White. He found the sac was composed of connective tissue lined by endothelial cells; the pedicle contained one artery and one vein. The main structures of the tumour can be seen in cross section (Fig. 3). Within the discs of cartilage and pre-cartilage which separate the vertebræ were mucoid foci but nothing which could justifiably be termed notochord remnants. There was a spinal canal, meninges, and a spinal cord. There were loops of intestine suspended within an endothelial lined cavity, adrenals, and testes composed of seminiferous tubules but no efferent ducts.

Case II.—On 27.7.39, at the Coventry and Warwickshire Hospital, Mr. Morton Anderson successfully removed an included fœtus from the abdomen of a 5 weeks' old girl, who had had abdominal enlargement since birth. A pre-operative X-ray of her abdomen showed a vertebrate skeleton within the tumour, and it was found that an antenatal X-ray of the mother's abdomen taken at 7 months' gestation showed her fœtus and the *fœtus in fœtu* (*see* Fig. 4). The X-ray of the specimen is shown in Fig. 5.

FIG. 4 (*Case II*).—X-ray of mother's abdomen at 7 months' gestation, showing fœtus and *fœtus in fœtu*. By courtesy of Mr. Morton Anderson (1950).

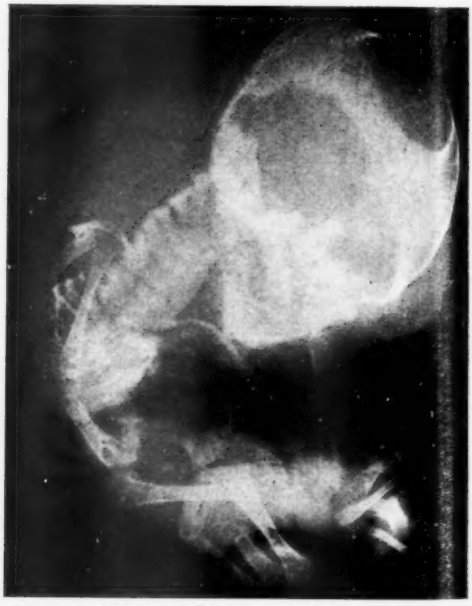

FIG. 5. (*Case II*).—X-ray of *fœtus in fœtu* removed at operation from a girl of 5 weeks. By courtesy of Mr. Morton Anderson and the *Nursing Times*.

The tumour was encapsulated and pedunculated, the pedicle running towards the host's liver.

These two specimens of *fœtus in fœtu* show a vertebrate organization. It therefore seems reasonable to believe that they developed through the primitive streak stage of embryogenesis and are, in fact, included twins—that is malformations and not neoplasms.

Such cases have not previously been studied. It has generally been assumed (in spite of the work of Nicholson, 1934, 1935, and of Willis, 1948) that all teratomas are included twins and that a *fœtus in fœtu* is just a very fœtiform teratoma. Therefore no individual specimen of *fœtus in fœtu* has been published with studies proving its vertebrate nature.

This series.—It has been possible to collect 7 additional cases that appear to have been vertebrate, and 10 cases of indubitable fœtiform teratoma. No teratoma showed any evidence of vertebrate organization. No *fœtus in fœtu* possessed teratomatous structures—further evidence that the *fœtus in fœtu* is not neoplastic.

It is noticeable that the prognosis is far better in cases of *fœtus in fœtu* than of fœtiform teratoma (*see* Tables I and II). Of the cases that occurred in the nineteenth century and which were not treated surgically all 5 children with teratomatas died during the first year of life. Amongst the cases treated surgically 2 cases out of 5 teratomas survived, while of 6 cases of *fœtus in fœtu* 5 survived.

TABLE I.—CASES NOT TREATED SURGICALLY

Author and date of necropsy	Sex of host	Swelling seen	Age at death	Cause of death
Fœtiform teratomas				
Fattori, 1810	F	At birth	Stillborn	—
Schaumann, 1837	F	At birth	Stillborn	—
Buhl, 1859	F	At birth	4 hours	Atelectasis
Kolisko, 1890	?	Early	5 weeks	Fever and bronchitis
Prochaska, 1813	F	Before 3 months	8 months	Vomiting
Fœtus in fœtu				
Klebs, 1876	M	After birth	Few weeks	Peritonitis
Young, 1808	M	After birth	9 months	Vomiting
Highmore, 1814	M	7 years	15½ years	Sepsis, perforation into intestine

TABLE II.—CASES TREATED SURGICALLY

Author and date of operation	Sex of host	Swelling seen	Age at operation	Result
Fœtiform teratomas				
Budde, 1926	M	3 days	2 months	Died
Ford and Hittner, 1948	F	7 months	17 months	Died
Rosenbach, 1906	M	3 years	3 years	Died
Williams, 1930	F	2 months	7 months	Lived
Haberer, 1939	F	4 years	5 years	Lived (nephrectomy)
Fœtus in fœtu				
Anderson, 1939 (*see* Davis, 1939)	F	At birth	5 weeks	Lived
Gross and Clatworthy, 1947	F	At birth	5 days	Lived ("Twin fœtuses *in fœtu*")
Lord, 1950	M	9 days	7 weeks	Lived
Maxwell, 1940	F	3 months	4 months	Lived
Brunkow, 1937	F	9 months	14 months	Lived
Hoeven, 1943 (*see* Potter, 1952)	M	12 months	15 months	Died (nephrectomy)

Sites and attachments of fœtus in fœtu *and fœtiform teratomas.*—This difference in prognosis is related to the attachments of the tumours. The teratoma is a polycystic tumour, usually without a definitive capsule or pedicle. It is attached by a broad base to the posterior abdominal wall and often lies behind vital structures. The *fœtus in fœtu* on the other hand is always encapsulated and in 8 cases out of 9 was pedunculated. Fœtiform teratomas sometimes, and *fœtus in fœtu* almost invariably, are attached near the origin of the superior mesenteric vessels. No direct communication of the pedicle blood vessels of the *fœtus in fœtu* with those of the host was found but often a plexus of vessels was present in the posterior sac wall.

Clinical aspects of fœtus in fœtu.—Abdominal enlargement is the presenting symptom. Pressure symptoms tend to be less acute than in the cases of fœtiform teratoma. An analysis of the symptoms in the 9 cases shows that the younger the patient when the tumour is observed the more likely he is to develop symptoms of pressure—dyspnœa, vomiting and pain. A rapid increase in the size of the tumour is a danger signal, whether it be due to an increase in capsular fluid or to gangrene and sepsis

of the tumour. Other untoward symptoms are fever, pain, and signs of peritoneal irritation. In the absence of these signs treatment is not a matter of urgency, but operation should be performed early in life before secondary adhesions form.

A teratoma, however fœtiform, is potentially malignant and removal must be radical. In cases of *fœtus in fœtu* heroic surgery is not essential and if necessary the sac may safely be left in situ. The eldest of the patients so treated, that of Brunkow (1942), is healthy at 15 years. The removal of a pedunculated tumour from within its sac is a relatively safe procedure in young babies.

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Section of Pathology

President—Professor G. PAYLING WRIGHT, D.M., F.R.C.P.

[*March* 16, 1954]

DISCUSSION: THE PATHOLOGY OF SPONTANEOUS INTRACRANIAL HÆMORRHAGE

Professor Dorothy S. Russell (Bernhard Baron Institute, The London Hospital, E.1):

Spontaneous Intracranial Hæmorrhage

The qualification "Spontaneous" in the title of this discussion eliminates all varieties in which trauma plays a part. To narrow the field still further I propose to exclude the neo-natal period. In addition I shall omit the numerous and varied conditions in which the brain is the site of multiple small hæmorrhages, and confine myself to significant large hæmorrhages. In assessing what is significantly large it is of course necessary to relate size to the site: a relatively small focus may be of fatal consequence in the brain-stem, but one of similar size in the cerebrum may be compatible with survival.

In the following analysis[1] of intracranial hæmorrhages, occurring in the necropsy records of the London Hospital in the period 1912-1952, an arbitrary limit of 1·5 cm. was fixed for the lower limit of hæmorrhages in the brain-stem, and 3 cm. for the cerebrum and cerebellum. In examples that approximated closely to these dimensions the clinical notes were helpful in assessing their significance and hence their inclusion or exclusion.

Table I gives the total number of cases and the main categories in their analysis. The *hypertensive group* constitutes about 50% of the total. The majority here (155, or 67%) were diagnosed as benign hypertension; the rest (77, or 33%) as either malignant (M.H.T.) or nephritic hypertension. These figures are only approximate since the diagnosis for the earlier decades often rests upon the macroscopic appearances of the kidneys and the age of the patient. Many in the benign group were elderly subjects with gross vascular degeneration and only slight or moderate degrees of cardiac hypertrophy. *Congenital defects in the media* of the main cerebral arteries led to the formation and subsequent rupture of a berry aneurysm in 92, and rupture without aneurysm in 4, totalling 96.

TABLE I

I.	Hypertensive	232
II.	Congenital medial defects in cerebral arteries (92 cases with aneurysm)	96
III.	Blood diseases	36
IV.	Mycotic aneurysm	28
V.	Vascular hamartoma	21
VI.	Arteritis (no aneurysm)	13
VII.	Neoplasms	9
VIII.	Arterial degeneration (No cardiovascular hypertrophy)	7
IX.	Various	3
X.	Cause not found	16
	Total	461

In the group of *blood-diseases* acute leukæmia was responsible for major hæmorrhage in 15 cases, thrombopenia in 13, aplastic anæmia in 3, other anæmias in 3, erythrocythæmia in 1 and hæmophilia in 1.

Neoplasms, which include both primary and secondary growths, form a surprisingly small group in view both of their considerable number in our necropsy material and current conceptions concerning their liability to give rise to spontaneous hæmorrhages of significant size.

Arteritis in Table I signifies purulent inflammation and rupture without aneurysm-formation. This was due to pyæmia in 10 examples. In 3 it complicated purulent leptomeningitis. It is of interest that polyarteritis nodosa finds no place in this series. Our sole example as a cause of hæmorrhage involved the spinal cord.

[1]I am greatly indebted to my Assistants, Dr. C. W. M. Adams and Dr. D. Ireland-Jones for their help in this.

The study of intracranial hæmorrhage from the point of view of its anatomical situation leads to the separation of groups involving (1) the subdural space, (2) the leptomeninges and (3) brain substance. In many instances, however, the hæmorrhage is not confined to one level.

(1) *Subdural hæmorrhage.*—Accepting the view that the subdural hæmatomas of middle-aged and elderly subjects are the result of trauma, in the absence of other causes demonstrated at necropsy, there are only 23 non-traumatic cases in our series where the subdural space formed the main site. Blood-diseases accounted for 11 of these; congenital aneurysms for 7; mycotic aneurysms for 2 and neoplasms for 3.

(2) *Subarachnoid hæmorrhage.*—The principal cause is rupture of a berry aneurysm. Mycotic aneurysms, blood diseases and persistent hypertension may also be responsible for primary subarachnoid hæmorrhage, and some of those for which a cause was not found fall also into this group.

Histopathology of congenital aneurysms.—Though it is generally accepted that their formation is based upon a congenital defect in the media of the main cerebral arteries it has been widely contended that the secondary factors of hypertension and focal degeneration of the arterial wall play an important part both in the evolution of the aneurysm and in its subsequent rupture. Our figures confirm the growing recognition that this is a catastrophe of middle-age rather than of the early decades. The greatest incidence of rupture is in the fifth and sixth decades; there are no proved examples with rupture in the present series below the third decade. Cardiac hypertrophy was recorded in 12 of the 96 examples. From these considerations, and from the prevalence of demonstrable degenerative changes in the wall of the sac it is difficult to escape the conclusion that these secondary factors are of paramount importance. But the argument that the basic pathology is a congenital defect in the media is supported by the demonstration of associated defects of a similar character without degeneration, and at sites remote from branching, in the splanchnic arteries.

(3) *Brain. Hypertensive hæmorrhage.*—Table II shows the principal sites affected. The classical site in the basal ganglia, with rupture into the adjacent ventricle, accounts for most of the total of 232, and the numbers assigned to the benign and nephritic groups (including malignant hypertension) are roughly proportionate to the totals in these. In the cerebral white matter and cerebellum there is a preponderance in favour of benign hypertension, but this is definitely reversed in the brain-stem where malignant hypertension and nephritis collectively preponderate.

TABLE II.—HYPERTENSIVE: SITES

1.	Basal ganglia .. .. (Benign: 104)	151
2.	Cerebral white matter .. .. (Benign: 17)	21
3.	Pons and mid-brain .. .. (Benign: 14)	32
4.	Cerebellum .. .. (Benign: 15)	18
5.	Subcortical: Cerebrum .. .. (Benign: 1)	4
6.	Meninges .. .. (Benign: 4)	6

The explanation for this rests upon the vascular pathology responsible for the hæmorrhage. In benign hypertension the perforating cerebral arteries show a replacement of the muscle of the medial coat by fibrous tissue. Atheroma in the intima may lead to thrombosis rather than rupture but, in the absence of gross atheroma, rupture is apt to occur. This of course is deduced from the appearance of arteries seen in the neighbourhood of a hæmorrhage; the chances of observing the vessel or vessels that are actually responsible for the catastrophe are remote. The pathology of such vessels has been the subject of controversy since the time (1868) that Charcot and Bouchard ascribed apoplexy to miliary (more accurately sub-miliary) aneurysms. When it was later demonstrated that these so-called aneurysms were in reality either subadventitial hæmorrhages, or extravascular clots, the view gained currency that these formations were the result of hæmorrhage and not a predisposing cause. Actually sub-miliary aneurysms can occasionally be demonstrated upon the perforating arteries, as reported by Green (1930) who found one in each of two cases in the careful examination of 10 hypertensive subjects. The vessels concerned, as illustrated in his colour-plate, are in obvious degeneration; leakage of blood is demonstrated by pigment in the adjacent tissues.

In malignant hypertension the characteristic form of arterial and, especially, arteriolar degeneration is a fibrinoid necrosis ("necrotising arteritis") (Fig. 1). A fluffy zone of exudate with similar staining properties often extends beyond the adventitia. Though this change may be widely dispersed in the vessels of the cerebral cortex and subjacent white matter, and associated then with the punctiform or larger hæmorrhages and œdema that go with "hypertensive encephalopathy", the pons is affected with remarkable frequency even when little is demonstrable elsewhere in the brain. It is therefore suggested that this is the reason for the predominance of pontine hæmorrhage in the malignant and nephritic forms of persistent hypertension.

Furthermore it may reasonably be argued that this individual form of degeneration is based upon *vascular spasm*. In support of this it is only necessary to quote two sets of experiments by Byrom: (1) The production of necrotising arteritis in rats by the injection of repeated doses of vasopressin (1937); (2) the direct observation of arterial spasm in the cerebral arteries of the living animal, in association with malignant hypertension, as quoted by Clifford Wilson (1953) in his Oliver-Sharpey lectures.

In 7 of our cases cerebral hæmorrhage was caused by arterial degeneration of the benign hypertensive type in the absence of persistent hypertension and cardiovascular hypertrophy. These were all in the sixth decade and later. Two will be illustrated. (1) P.M. 39/36, a male aged 55. The hæmorrhage formed a large mass, measuring 6 cm. from before back, beneath the hind end of the island of Reil and extending back into the occipital lobe (Fig. 2). The onset of referable neurological disturbance had been sudden, at 2 months before death, and the character of the clot, which was brown and pultaceous, agreed with this history. Dissection of the regional vessels revealed no alternative cause for the condition. Microscopically the border of the hæmorrhage gives evidence of chronic inflammatory reaction, moderate gliosis and free iron in macrophages. Death was precipitated by arteriography, using thorotrast. (2) P.M. 339/51, a male aged 79 (Fig. 3). Right hemiplegia occurred suddenly two days after prostatectomy. Though he subsequently improved slightly his speech was affected and he died in hospital 5 months later from pulmonary embolism. This hæmorrhage (5 cm. in its greatest dimension) has undergone surprisingly little change in spite of its duration and, although there is some increase of collagenous tissue at the periphery, it has certainly not reached the stage of encapsulation.

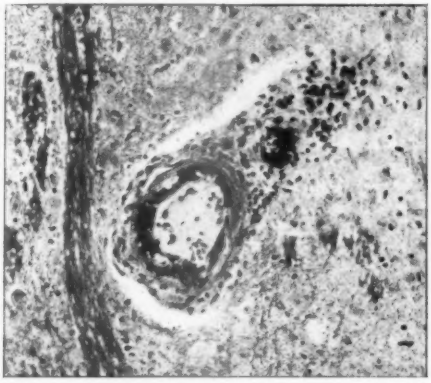

FIG. 1.—Perforating artery of pons showing early stage of fibrinoid change (black) in malignant hypertension Phosphotungstic-acid hæmatoxylin. × 114.

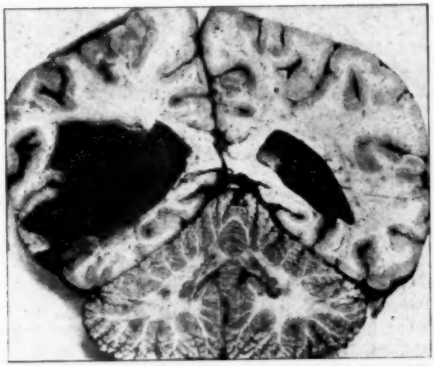

FIG. 2.—Coronal section of brain (P.M. 39.1936). The hæmorrhage reaches the ventricular wall but has not ruptured it.

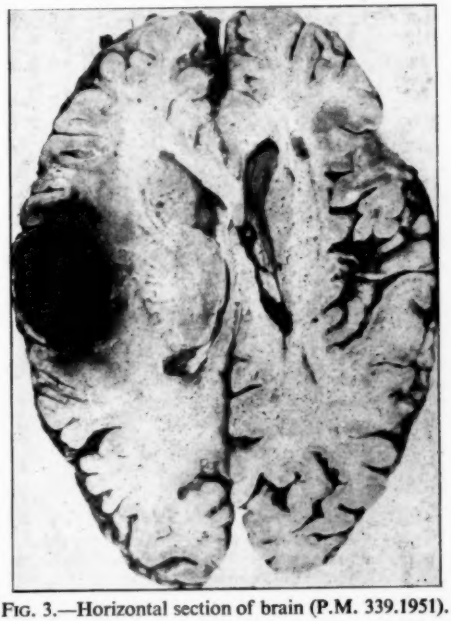

FIG. 3.—Horizontal section of brain (P.M. 339.1951).

Vascular hamartomas.—Any of the recognized types of vascular hamartoma can give rise to spontaneous hæmorrhage.

(1) *Telangiectases.*—These, of essentially capillary structure, are most often found in the pons. They are usually a chance necropsy finding, unsuspected clinically. Spontaneous hæmorrhage has rarely been recorded as a complication, and none occurs in our series.

(2) *Cavernous hæmangioma.*—These favour a subcortical site in the Rolandic area, the basal ganglia and less commonly other parts of the brain. In occasional examples they are multiple. Blood can certainly ooze from them producing pigmentation of the neighbouring tissues, but major hæmorrhages are very rare. In the present series there is one example of multiple cavernous hamartoma (P.M. 441/47, a male aged 56) where the symptoms of a third-nerve palsy and slight extravasation of blood into the C.S.F. suggested the diagnosis of a leaking berry aneurysm on the circle of Willis, and craniotomy was performed on the strength of this. The brain in this case revealed a large number of widely scattered cavernous foci (42 in all) of different sizes. The largest occupied the corpus callosum and foramen of Luschka respectively and were probably responsible for the hæmorrhage. A unique feature was the presence, in the left third nerve, of a small cavernous lesion which was responsible for the palsy.

(3) *Arterio-venous hamartoma.*—This form of vascular anomaly is a notable source of spontaneous hæmorrhage, and is responsible for 20 of the 21 cases of the series classified as vascular hamartoma. These lesions manifest themselves in early life, the majority (7) being found during the 2nd decade followed by the 1st (4 cases), 3rd and 4th decades (3 each). The classical type is the formidable tortuous mass of arteries and veins in the meninges of the middle cerebral area of supply, which burrows into the subjacent brain and may eventually rupture into the lateral ventricle, or produce a hæmatoma in the cerebral substance. These, however, produce symptoms—convulsive attacks, audible bruit and so forth, which lead to their detection. Though sometimes observed in childhood, the examples in our series, with or without hæmorrhage, have been in young or middle-aged adults.

I wish to draw particular attention to a group of small lesions of this kind which, without premonition, may give rise to sudden large and fatal hæmorrhage. They are found in our experience at the following sites :—

(1) *Cerebral convexity*, sometimes concealed in the depths of a sulcus and perhaps involving the adjacent cortex and subcortical white matter more extensively than the meninges. Illustration is provided by a case in which the hamartoma happened to be readily visible on inspection of the brain at necropsy. This was from a woman, aged 32, who was pregnant at 32 weeks. She had suffered from excessive vomiting. Sudden onset of headache, with giddiness, vomiting and collapse led on to deep coma and spasticity of all limbs. Blood was found in the C.S.F. on lumbar puncture. A left sub-temporal decompression revealed a small subdural hæmatoma. She died 4 days after the onset. At necropsy a massive hæmorrhage extended in the white matter of the left cerebrum from the temporal horn to the occipital pole. This was related to a small tangle of vessels in the meninges over the ventral aspect of the temporo-occipital region, supplied by a branch of the posterior cerebral artery; the veins drained towards the lateral border of the hemisphere.

Microscopically, enlarged tortuous and malformed arteries and veins penetrate the brain substance (Fig. 4).

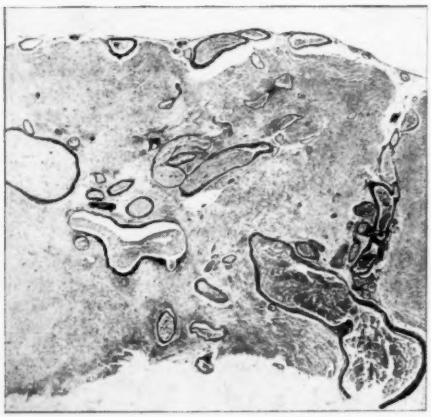

FIG. 4.—Cortex of temporo-occipital region, showing penetration by enlarged tortuous arteries and veins (P.M. 408.1948). Phosphotungstic-acid hæmatoxylin. × 5·5.

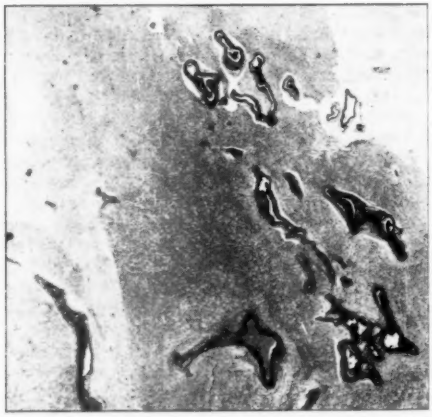

FIG. 5.—Arteriovenous hamartoma near head of caudate nucleus in boy aged 11 (P.M. 295.1938). Masson's trichrome. × 5·6.

Though this example is from an adult, it has been our experience that what might be termed the cryptic type of case seems most often to occur in children. In fact 11 of my 20 arteriovenous hamartomas are from subjects ranging from 16 years downwards. The onset is always catastrophic: the

"bolt from the blue", without warning, and death within 24 to 48 hours as a rule. In 4 of these 11 cases the lesion has lain in the middle cerebral area of supply.

(2) In 5 the hamartoma has been central, predominantly venous, and affecting part or the whole of the pathway leading from the choroid plexus of a lateral ventricle, the vein of the corpus striatum and lesser vein of Galen. This lesion may be obvious from its magnitude on dissection of the brain; on the other hand, it may be so small that it can be missed. In illustration of this I would quote the case of a boy aged 11 (P.M.295/38) who collapsed at school in the manner already described. A massive recent hæmorrhage occupied the white matter from the frontal region to the coronal level of the splenium of the corpus callosum. A tributary of the vein of the corpus striatum, crossing the head of the caudate nucleus was enlarged but no abnormal artery could be seen. On section a small group of vessels with thickened walls lay between the abnormal vein and the border of the hæmorrhage, the area measuring 0·7 × 0·5 cm. Microscopically this was confirmed (Fig. 5). Stains for elastic fibres demonstrated that arteries as well as veins contributed to the hamartoma. This introduces the question as to whether pure venous malformations do in fact exist. They have been described in the literature by many authorities. Though some of our examples are predominantly venous, an arterial element has been constantly found on microscopic examination. This does not imply the presence of arteries which might be interpreted simply as incidental, but that these arteries are abnormal both in size and structure.

(3) The third site of importance is the *cerebellum*, accounting for 2 of our 11 cases. Again the lesion may be remarkably inconspicuous. I have encountered several unruptured, and thus clinically silent, examples of this kind as chance necropsy findings. They have occupied the central white matter of a lateral lobe, measuring only a few millimetres in diameter.

It is thus understandable that, in some cases, the lesion responsible for a large spontaneous hæmorrhage may itself be destroyed in the event. It is more than likely that some of our cases in the category "cause not found" are of this kind, and in particular those of the early decades. In life the venturesome neurosurgeon nowadays may successfully evacuate the hæmorrhage, as described in recent articles by Miss Beck (1953) and by Werner (1954). Miss Beck will deal further with this subject.

The pathologist, on the other hand, is best advised also to evacuate the clot, and thereafter to fix the brain before attempting to discover these small lesions. The multiplicity of petechiæ in the softened tissue about the main hæmorrhage makes this in any event a difficult task, but a hand-lens will help in the detection of tortuous vessels with thickened walls.

Frequent as the cryptic hamartomas appear to be in relation to fatal hæmorrhage, there is little about them in the literature. A good account is however given by Margolis *et al.* (1951) who reviewed the subject and reported a series of 4 cases.

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Mr. M. A. Falconer (Director, Guy's-Maudsley Neurosurgical Unit, London):

Surgical Pathology of Spontaneous Intracranial Hæmorrhage Due to Aneurysms and Arteriovenous Malformations

Until recently our knowledge of this subject was based largely upon autopsy findings. However, the increasing use of cerebral arteriography and the advances of neurosurgery have enabled us not only to demonstrate during life most cerebral aneurysms and arteriovenous malformations, but also to treat them successfully. Consequently we are becoming aware of aspects of their pathology that are not readily apparent in autopsy material alone.

Case-material.—This study is based upon 148 consecutive patients with spontaneous "subarachnoid" hæmorrhage, investigated under my care during the eight years up to January 1954. The diagnosis of subarachnoid hæmorrhage requires qualification for often there is intracerebral, intraventricular, and even subdural bleeding as well. Two characteristic features are, firstly, a sudden or rapid onset of headache with or without impaired consciousness, but with perhaps a stiff neck and kernigism, and secondly, the presence of blood in the cerebrospinal fluid. Often neurological signs, such as a third cranial nerve palsy, hemiparesis, aphasia, or hemianopia, are also present, indicating focal

cerebral damage. However, cases with gross hemiplegia and coma, typically seen in middle-aged and elderly people with evidence of widespread arterial disease, were not included in my series, for in them a massive intracerebral hæmorrhage secondary to generalized vascular degenerative disease was presumed to be present. Furthermore, most cases of this type are quickly fatal.

The presence of blood in the C.S.F. was confirmed in most of my patients, but in a few in whom lumbar puncture was not performed during the acute stages, it was presumed from the clinical picture. The first 69 patients were investigated in New Zealand (Falconer, 1951), and the remainder in the Guy's-Maudsley Neurosurgical Unit (Falconer, 1952). All except Case I were investigated by carotid arteriography, generally performed bilaterally, while vertebral arteriograms were obtained in 10 of the 31 patients in whom carotid studies were normal. The following findings were made:

Intracranial aneurysms in	100	patients.
Arteriovenous malformations in	12	,,
Intracerebral hæmatomas without obvious cause in	7	,,
Cerebral tumours in	3	,,
No cause ascertained in	26*	,,
	148	patients

* 6 of these patients have since died, and at autopsy 4 were found to have saccular aneurysms (basilar artery 2, internal carotid artery 1, middle cerebral artery 1).

Hæmorrhage Due to Aneurysms

These findings support the prevailing view that leaking intracranial aneurysms are the commonest cause of spontaneous subarachnoid hæmorrhage, accounting for possibly three-quarters of all cases (Richardson and Hyland, 1941; Magee, 1943; Hamby, 1948). These lesions are still often erroneously termed ruptured "congenital" aneurysms, with the implication that they generally cause symptoms by sudden rupture in young persons. However, they are really acquired lesions occurring at a site of congenital weakness, and they do not usually cause symptoms until later life and then by seepage rather than by frank rupture. They are also multiple in more than 10% of cases. Histological evidence indicates that they arise from the interaction of two factors: (1) focal degenerative changes in the intima and elastica of the arterial wall, and (2) a congenital deficiency of the muscular layer, such as occurs typically at the angle of branching of an artery (Carmichael, 1950).

Forty-four of my patients with aneurysms were males and 56 females, a curious preponderance of females which has been noted by others and which is unexplained (U.K. Registrar-General's statistics; Ask-Upmark and Ingvar, 1950; Dinning and Falconer, 1953). In Table I the age-distribution of

PERCENTAGE AGE INCIDENCE

AGE –	10-19	20-29	30-39	40-49	50-59	60-69	70+
100 PATIENTS WITH DEMONSTRATED ANEURYSMS *present series*	5	15	17	28	22	11	2
118 HOSPITAL CASES OF SPONTANEOUS SUBARACHNOID HAEMORRHAGE *Richardson & Hyland's series*	3	13	18	25	21	16	3
250 CASES OF SUDDEN DEATH FROM RUPTURED ANEURYSM. *Keith Simpson's series*	2	3	8	14	23	28	22

Table I

these patients has been compared with that of a well-known unoperated series of hospital cases (Richardson and Hyland, 1941) and of a series of forensic cases in which bleeding aneurysms had caused sudden and unexpected natural death (Keith Simpson's series—Dinning and Falconer, 1953).

The age-distributions in the first two groups are identical, reaching their peak incidence during the fifth and sixth decades of life. In the forensic series, however, the peak incidence is delayed a decade or more later, indicating that death from aneurysms as opposed to morbidity usually occurs later in life, and in the same age-range as death from rupture of an arterio-sclerotic artery.

A total of 110 aneurysms were demonstrated in my 100 patients, multiple aneurysms being disclosed in 9. The distribution of all these aneurysms is depicted in Fig. 1, and conforms to established autopsy

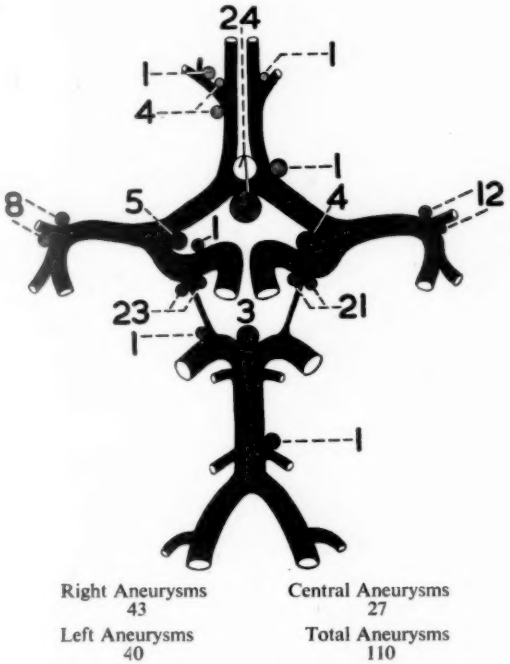


FIG 1.—Sites of aneurysms demonstrated angiographically in 100 patients.

patterns (Richardson and Hyland, 1941; Hamby, 1948). With 2 exceptions all the aneurysms were situated at an angle of branching of a major cerebral artery. The three principal sites were (*a*) the junction of the internal carotid artery and its posterior communicating branch, 44 examples, (*b*) the junction of the anterior communicating artery with either anterior cerebral artery, 24 examples, and (*c*) the first point of branching of the middle cerebral artery within the fissure of Sylvius, 20 examples. As these sites are all on the carotid arterial tree, carotid arteriography will demonstrate most aneurysms, whereas vertebral arteriography is required in only a few cases. Examples of arteriograms of aneurysms in various sites are shown in Figs. 2, 3, 4 and 5. Almost all the aneurysms encountered were between 0·2 and 1·5 cm. diameter, and in only 3 instances was the diameter 2 cm. or more. If necessary, most aneurysms can be readily exposed at operation without sacrificing any brain substance.

Intracranial aneurysms are associated with anomalies of the circle of Willis in, perhaps, as much as one-third of cases (personal observations). Thus in 8 of my 23 cases of aneurysm of the anterior communicating artery both anterior cerebral arteries distal to the communicating artery could be filled only from one carotid artery, indicating a deficiency in the circle (Fig. 3).

From histological evidence bleeding would usually appear to result from a dissecting process affecting the wall of the aneurysm, leading to seepage of blood, rather than from a frank rupture of the sac (Hyland and Barnett, 1954). Our operative findings support this view, for if an aneurysm is exposed at operation following a recent hæmorrhage, one often sees a red spot on its fundus suggesting an intramural hæmorrhage. A sudden burst occurring spontaneously would quickly be fatal, and may well account for a massive extravasation of blood throughout the subarachnoid spaces.

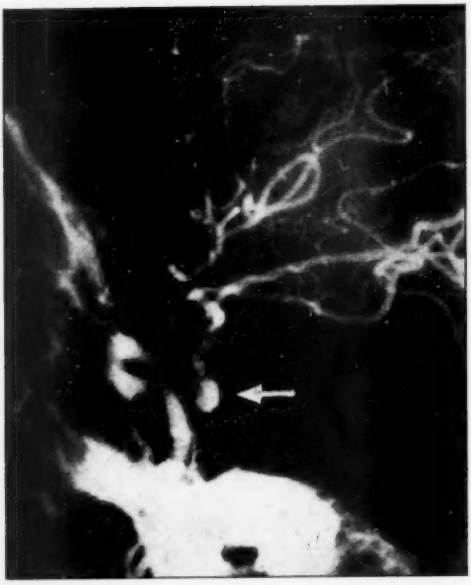


FIG. 2.—Aneurysm at junction of internal carotid and posterior communicating arteries (carotid arteriogram—lateral projection).

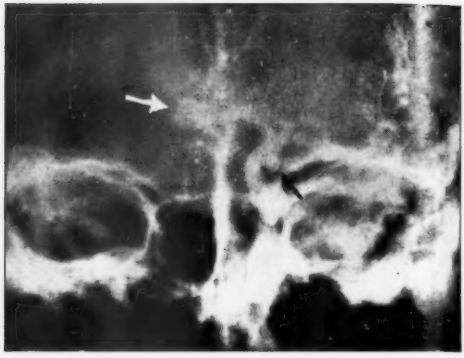


FIG. 3.—Two aneurysms, one (white arrow), arising from anterior communicating artery and the other (black arrow) at junction of internal carotid and posterior communicating arteries. Both were approached successfully at operation.

Such a massive extravasation is never seen at operation. Sizable but focal intracerebral and subdural hæmatomas may be encountered at operation, but as regards the subarachnoid space at the most one meets with only a little patchy clot. By and large therefore it is more correct to describe these

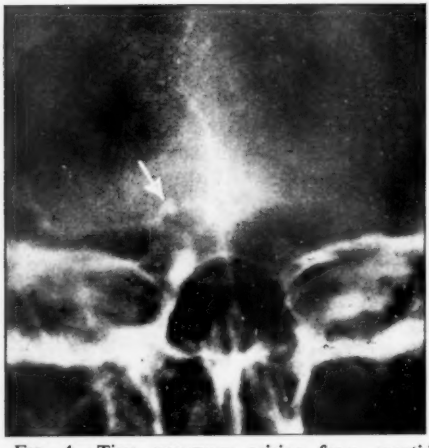


FIG. 4.—Tiny aneurysm arising from carotid bifurcation (carotid arteriogram—A.P. projection). Note also moderate degree of spasm of anterior and middle cerebral arteries.

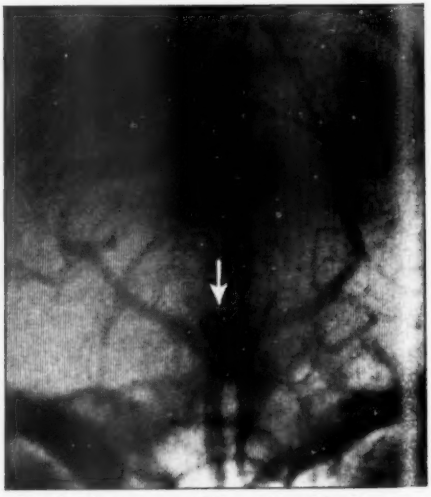
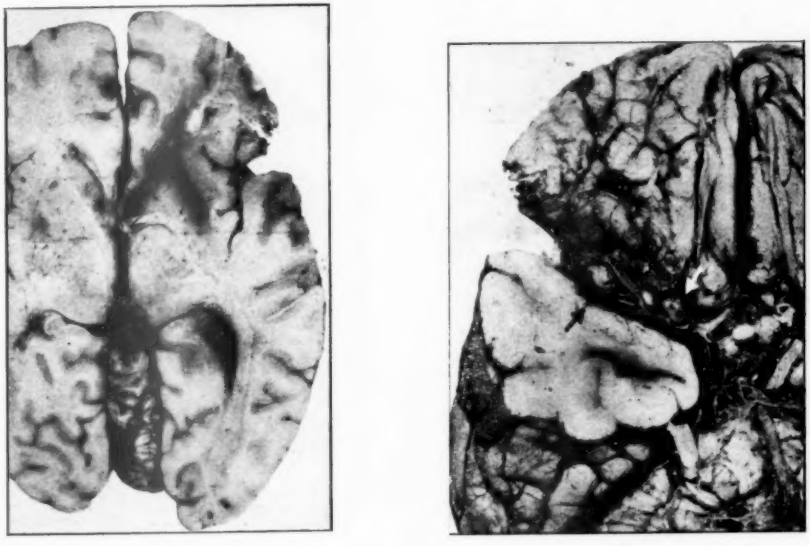


FIG. 5.—Aneurysm at bifurcation of basilar artery (vertebral arteriogram—A.P. projection).

aneurysms as "leaking" than as "ruptured", especially as the actual amount of blood which enters the cerebrospinal fluid, even in a marked case of subarachnoid hæmorrhage, may be as little as 3 c.c.

(Lindsay, 1950). Again symptoms of subarachnoid hæmorrhage seldom appear during strenuous exertion (Magee, 1943; Ask-Upmark and Ingvar, 1950; and personal observations). Possibly the dissecting process also accounts for this observation, for it may be that, although exertion may initiate the process, a period of time is required before the process is completed to the point of leakage. Arterial hypertension is not a significant factor, for its incidence is not appreciably raised in this condition.

Aneurysmal bleeding may occur not only into the subarachnoid space, but also into the cerebral substance and occasionally even into the subdural space. While many aneurysms of the circle of Willis lie within the basal cisterns, and so bleed primarily into the subarachnoid space, aneurysms on the distal arteries as well as those projecting upwards from the anterior communicating artery or from the carotid bifurcation tend to be surrounded by brain substance, and consequently bleed into the frontal or temporal lobes, and only secondarily burst into a ventricle or into the subarachnoid space (Fig. 6 A, B). At autopsy the causal aneurysm in such cases may be obscured, and unless the pathologist deliberately dissects the distal cerebral arteries he may not even suspect its presence.



A B

FIG. 6.—(A) Intraventricular hæmorrhage resulting from (B) aneurysm at carotid bifurcation (white arrow). Note absence of subarachnoid clot, and also second aneurysm (black arrow) on middle cerebral artery.

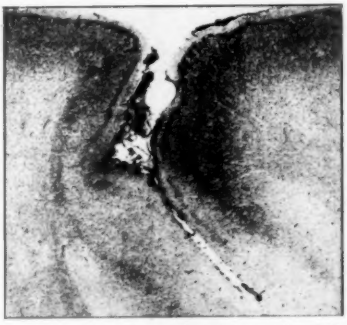


FIG. 7.—Section of frontal cortex showing focal necrosis of the cortex in the depth of a sulcus. Nissl. × 5·2.

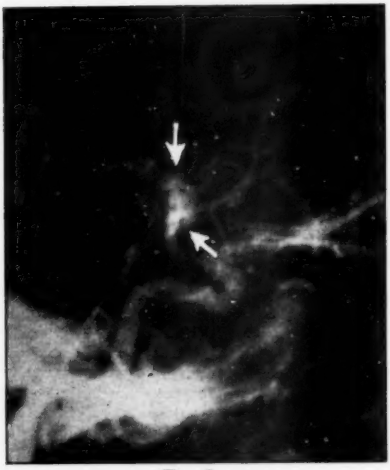


FIG. 8 A

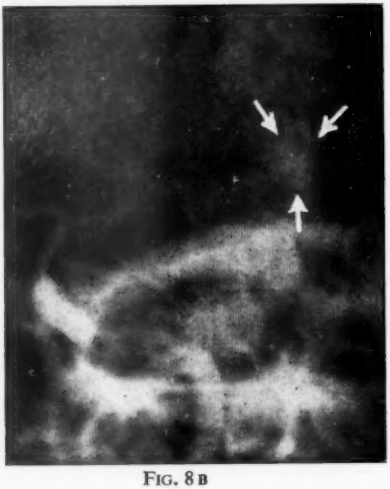


FIG. 8 B

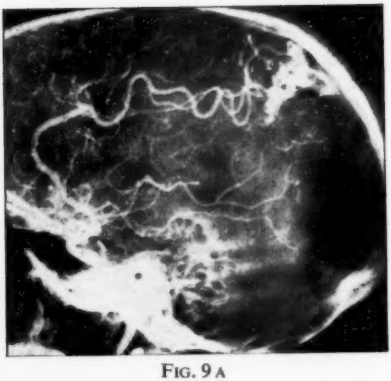


FIG. 9 A

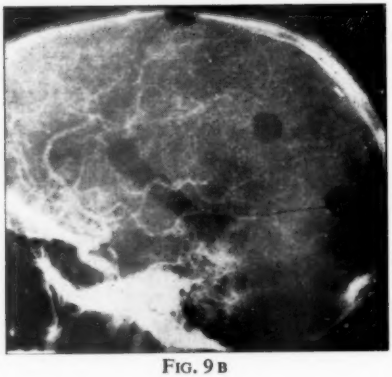


FIG. 9 B

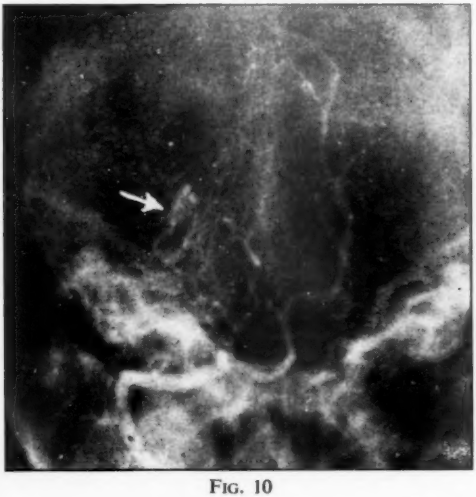


FIG. 10

FIG. 8. — Aneurysm of middle cerebral artery associated with gross vasospasm (carotid arteriograms—(A) lateral and (B) A.P. projections). Notice marked narrowing of terminal portion of internal carotid artery and of anterior cerebral artery, while middle cerebral artery is so grossly attenuated as to be almost invisible.

FIG. 9. — (A) Arteriovenous malformation at termination of anterior cerebral artery. Note large calibre of artery, and also two large veins draining posteriorly from lesion. (B) Following excision of lesion the calibre of the anterior cerebral artery has resumed its proper proportions, while the draining veins are no longer filled.

FIG. 10.—Arteriovenous malformation of right superior cerebellar artery (vertebral arteriogram —A.P. projection). This was successfully operated on by proximal clipping of the feeding artery.

Occasionally an aneurysm may bleed into the subdural space either by direct contact or by rupture of an intracerebral hæmatoma on the surface of the brain (Logue, 1951; Clarke and Walton, 1953); there were two examples in my series, both successfully treated. Arteriography often gives a clue to the presence of these intracerebral and subdural hæmatomas.

There is yet another mechanism by which leaking aneurysms can produce symptoms; this involves the associated vasospasm. As Graeme Robertson (1949) has pointed out, focal necrosis can occur in subarachnoid hæmorrhage at sites remote from the aneurysmal lesion, and without an obvious reason like intracerebral hæmorrhage or arterial thrombosis. A good example of this was found in a case of leaking aneurysm of the left anterior cerebral artery in which death took place, without any arteriographic or operative intervention, 6 days after the onset of symptoms. At autopsy (Dr. A. L. Woolf) the bleeding was entirely subarachnoid, and there was no thrombosis or obvious obstruction of any cerebral artery. Yet a patch of cortical necrosis was found in the territory of the left middle cerebral artery (Fig. 7). To explain such a finding Robertson postulated cerebral vasospasm. Arteriographic evidence of the existence of such spasm is often forthcoming if the investigation is undertaken during the stage of acute symptoms. An instance is furnished by Fig. 8 A, B, where arteriography performed within two days of the onset of symptoms showed gross constriction of the middle cerebral artery supplying the aneurysm, as well as marked but lesser constriction of the terminal portion of the internal carotid artery and of the anterior cerebral artery. Ecker and Riemenschneider (1951) and Norlén and Olivecrona (1953), like myself, have seen such spasm of the cerebral arteries fairly often with recent intracranial hæmorrhage, but not in the quiescent stages, nor in cerebral tumour material. Neurophysiologists hold that the only local stimulus which will send an artery into contraction is a traumatic one. Perhaps the dissecting process in the wall of the aneurysm is such a stimulus, for it seems likely that this spasm acts as a local protective reflex which limits and halts the seepage of blood. It may also account for the high rate of fatalities and hemiplegia that complicate carotid ligation performed in the presence of recent hæmorrhage (Schorstein, 1940). Further, it may explain why attempts at carotid arteriography within a few days of bleeding are liable to be followed by a transient hemiparesis. Hence I now, whenever possible, defer cerebral arteriography for a week to 10 days after the last hæmorrhage, an interval which is short of the period—2 to 4 weeks after the initial attack—when the risks of recurrent bleeding are at their highest.

Hitherto the prognosis of bleeding aneurysms has been deadly, and statistics from various sources confirm the dictum of Ask-Upmark and Ingvar (1950) that out of 5 patients with subarachnoid hæmorrhage treated conservatively, three will die sooner or later from its effects, one will be left crippled, and only one will make a good recovery. The future lies in timely surgical intervention, and the various points considered here are all pertinent. Considerations of operative technique are outside this paper, but it may be permissible to say that 96 of my 100 patients were submitted to carotid or vertebral ligation and/or to an intracranial attack on the aneurysm, with 13 deaths (mortality rate 13%) and with 13 instances of marked residual disability. However, since adopting, in December 1951, the policy of delaying arteriography and operation whenever possible for a week or more after the last hæmorrhage, as well as of using arterial hypotensive anæsthetic techniques, the last 32 of these patients have been operated upon with only 1 death (3% mortality), 2 instances of residual hemiplegia (6% disability), and 2 instances of marked mental slowing similar to that seen after leucotomy—27 cases (84%) made a good recovery. The surgery of leaking intracranial aneurysms is thus passing into the stage of consolidation.

Hæmorrhage Due to Arteriovenous Malformations

These lesions are the second common cause of subarachnoid hæmorrhage, accounting for possibly 5% to 10% of cases. More malformations manifest themselves by epilepsy than by hæmorrhage, but when they do bleed the clinical picture is often indistinguishable from that of subarachnoid hæmorrhage due to leaking aneurysm; any differences are qualitative rather than absolute. The association with epilepsy, the occurrence of bleeding in childhood, or a history of attacks of bleeding extending over many years, is more suggestive of malformation than of aneurysm. No very large series of cases has yet been reported. Of my 12 cases, 11 were in females and only 1 in a male, while their ages ranged from 3 years to 44 years. Mackenzie (1953), however, in his 12 cases observed an equal sex incidence with an age range of between 15 and 45 years.

Professor Russell has dealt with the pathological considerations of these lesions. They are really arteriovenous fistulæ, and can usually be readily shown by arteriography (Figs. 9 A, B and 10). A striking feature is that the main feeding artery or arteries is of larger bore than the neighbouring cortical arteries, and shunts arterial blood directly into large dilated veins, so that the malformation is fed with blood at the expense of the rest of the brain. This is clearly confirmed when angiographic studies are repeated after excision of one of these lesions (Fig. 9).

Thanks to the pioneering work of Olivecrona and Riives (1948), of Norlén (1949), of McKissock (1950) and of Jaegar (1950) the surgical treatment of these lesions has now become standardized (Falconer, 1952). The procedure of election is excision of the malformation, and this is generally practicable with lesions affecting the convexity of the hemispheres. Where it is not practicable, as

in deep-seated lesions, the feeding artery can be clipped and any associated intracerebral clot evacuated (e.g. Fig. 10). All my 12 cases were benefited by operation, and all survived.

I wish to thank my colleagues, Dr. A. C. Begg and Dr. R. D. Hoare, for the arteriographic studies, Miss S. Treadgold for Fig. 1, and Mr. C. E. Engel for most of the photographic reproductions.

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Miss Diana J. K. Beck (Department of Neurosurgery, The Middlesex Hospital, London):

Operable Intracranial Hæmorrhage

In the past three and a half years I have operated on 11 consecutive cases of intracerebral hæmorrhage. I shall give an account of the pathology of this condition in the living, and shall make no more reference to surgery than is necessary to emphasize that timely and appropriate surgical intervention saves lives and certainly diminishes residual disability.

The ages of these patients ranged from 35 to 62 years; 8 were women and 3 men. It is of interest that all but one of these hæmorrhages lay within the territory of the middle cerebral artery.[1] 7 were left-sided, 3 temporal, 2 lower parietal, 1 mid-Rolandic and 1 inferior frontal. Of the 4 situated in the right hemisphere, 3 were frontal and 1 occipital.

All of these patients presented as acute cerebrovascular catastrophes; 2 had been aware of abnormal phenomena such as transitory speech disturbance, weakness or paræsthesiæ in a limb in the preceding weeks or months, so that the possibility of hæmorrhage into a neoplasm had to be considered. Headache had been experienced by all. The conscious state varied from drowsiness to coma. In 3 Cheyne-Stokes' respiration was present. In all but 1, the occipito-temporal, there was hemiplegia of varying degree, often profound and sometimes complete. Complete hemiplegia and complete hemianæsthesia were present in 1 case. Sensory disorders were demonstrable in the lower parietal lesions, and in these and in those in the temporal and occipito-temporal regions, there was hemianopia as judged by the confrontation test. 8 of the patients had been aphasic before lapsing into unconsciousness.

All of these patients were seriously ill, 9 desperately so; it seemed almost unwarranted to intervene in those with Cheyne-Stokes' respiration.

[1] Since reading this paper, one patient, the subject of long-standing hypertension, has died of a massive right cerebellar hæmorrhage nearly three years after a large left temporal hæmatoma was removed.

8 had a high blood-pressure when first seen, ranging from 270/170 to 180/120. 3 of the 11 still have, and all of these were known to be hypertensive before operation.

Lumbar puncture was performed in 9; the fluid was blood-stained in 5, usually deeply so; in 2 ventricular puncture was necessary as part of the operative procedure; in these the fluid was xanthochromic and in each the protein content was raised, 70 mg.% and 140 mg.%. In 1 patient from whom an excessive amount of clear cerebrospinal fluid had been removed, the lumbar puncture resulted in tentorial herniation; in this instance the protein was 55 mg.%, there were two red blood corpuscles per cmm. and an unexplained pleocytosis of 78 lymphocytes per cmm.

In every case a clinical diagnosis was made of the presence and situation of an intracerebral hæmorrhage, confirmed by angiography in 10 cases. In some the angiograms were of poor quality, not because of technical imperfections but, I think, because of ischæmia associated with a rapidly expanding lesion or because of compression, thrombosis or spasm of vessels. In 1 case in which angiography suggested a subdural and an intracerebral clot, ventriculography demonstrated a communication between the ventricle and the clot-containing cavity.

The operative procedure consisted in each case in turning an appropriate osteoplastic flap to expose the cortex. The hæmatoma was completely removed in 9 through a transcortical incision and in the other 2 by tapping through the cortex; in these 2 the collection was fluid and the saline used for gentle irrigation of the cavity returned clear. Solid clot was removed by a combination of natural extrusion, suction and the use of pituitary rongeurs.

Operative Findings.—Six of these hæmorrhages were subcortical and 5 were deep, i.e., the surface of the clot was 3 cm. or more from the cortical surface.

In some, ventricular tapping or the use of 50% sucrose intravenously was necessary for safe opening of the dura.

The appearances varied according as the hæmorrhage was subcortical or deep. In the subcortical group, the exposed brain was highly congested, tense and without pulsation. Thrombosed veins were seen in some with linear hæmorrhages alongside. Localized bulging of a violet or plum colour was seen; sometimes there was yellow staining of the brain and in one instance the cortex was glazed and greenish in colour. The first sign of rupture of the clot through the arachnoid was observed in one case as a bead of coagulated blood. Although in the deep clots there was often congestion of superficial small vessels, it was noted that there was invariably widening and pallor of the gyri overlying the summit of the clot, and these also felt soft to the gently palpating finger. In one case a significant subdural clot had doubtless arisen from rupture of an intracerebral clot still in situ, for there was a ragged tear in the cortex. In three cases there were fragments of degenerate brain amongst the solid clot, but in all nine cases in which a transcortical incision was made, the remaining cavity was smooth and white-walled: it looked as though lined by ivory. The size of the cavity varied from $5 \times 4 \times 3$ cm. to $7 \times 6 \times 5$ cm.; in two of the largest there were in addition to solid clot 60 c.c. of dark fluid blood, and in a third 10 c.c. The contents of two cavities were entirely fluid. There was an active bleeding point seen in the depths of the cavity in 3 cases; only one of these was a hypertensive subject.

Results.—All these patients came under my care from three and a half years to four months ago. All have survived: the result is very good in one, good in eight, (all of these have returned to their normal occupations), fairly good in one and fair in one. I have not been able to relate in detail the dramatic stories of these patients, some of which have been recorded already (Beck, 1953). Although only three of these patients have remained hypertensive since operation, I have no doubt that the others harbour defects in the walls of their cerebral vessels and I should like to suggest that some at least have small angiomatous malformations not demonstrated by angiography.

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Dr. W. H. McMenemey (Department of Pathology, Maida Vale Hospital, London):

The Significance of Subarachnoid Bleeding

As a rule it is not difficult to distinguish true subarachnoid bleeding from normal fluid contaminated with blood shed by the diagnostic needle, especially if the fluid is collected in two, or preferably three, containers. In accidental puncture of a vein there will be decreasing amounts of blood in the three tubes as the needle is washed through by the cerebrospinal fluid. This is the most reliable method of

distinction. There are two less certain ways of telling: (1) the presence of xanthochromia in the centrifugalized supernatant fluid, which is usual in subarachnoid hæmorrhage; (2) the presence of a clot, which may occur with traumatic puncture of a vein.

If, however, lumbar puncture is resorted to within a few hours of the commencement of a subarachnoid hæmorrhage hæmolysis may not have developed; on the other hand xanthochromia may be seen in accidental hæmorrhage under three conditions: firstly, if the contamination is heavy and the erythrocyte count exceeds 150,000—200,000: the faintest trace of colour may then be noticed by reason of the liquid component of the contaminating blood, provided it is of average pigmentation; secondly, if for any reason—and amongst them we would list a precariously distended aneurysmal sac which has been responsible for recurrent incidents—the protein content before contamination has exceeded 150 mg. % and so has just appreciably tinged the fluid before the admixture of fresh blood; and thirdly, if perchance the receiving vessel has been contaminated by some markedly hæmolytic substance such as a detergent. But in addition to these three causes of xanthochromia one must keep in mind the possibility that one may be dealing with the fluid from an oozing aneurysm or a resolving hæmorrhage with the superimposed complication of a "bloody tap". Only a careful analysis of the contents of the three separate tubes will serve to recognize this mixture.

The presence of a clot in one or two of the tubes is strong evidence in favour of accidental bleeding, but it may only be expected if the erythrocyte count exceeds 200,000 (Badoux, 1951). It is seldom noted in true subarachnoid hæmorrhage unless the bleeding is torrential, and this is rare and always quickly fatal.

It seems to be the experience of most observers that blood will begin to hæmolyse in the subarachnoid space within twelve to twenty-four hours. Some authors, including French and Blake (1950) and Richardson and Hyland (1941), believe that on occasions hæmolysis may be delayed up to three or even four days; while others, including Merritt and Fremont-Smith (1937), are of the opinion that it may begin to show at four hours. Exactly how long erythrocytes may remain unhæmolysed in the lumbar sac is less easy to determine because it is not always possible to say when the aneurysm responsible for the initial bleed ceased to ooze; nor, in fact, can one exclude the possibility of a minor recurrence of bleeding or of a small independent bleeding due to congestion. The careful studies of Froin, made just fifty years ago, indicate that the process of hæmolysis of the erythrocytes is well advanced and often complete by the ninth day, and this I imagine is in accord with most people's experience. Richardson and Hyland (1941) found that, on average, erythrocytes had disappeared by the ninth day but in one case they were present on the nineteenth day. To some extent there would appear to be a quantitative factor involved, because the bigger the hæmorrhage the longer it takes to disappear.

The reason why erythrocytes lyse more quickly than one would expect, having regard to their known survival time in the bloodstream, is not clear. Swollen and ghost forms of erythrocytes are seen within a few hours of the beginning of the hæmorrhage, but only a minority of the cells is affected in this way. However, the hydrogen-ion concentration of cerebrospinal fluid rises rapidly once it has been withdrawn (Lange and Harris, 1944), so this fact must be taken into account when the erythrocytes are being studied in the laboratory. The milieu of the cerebrospinal fluid seems to be favourable for the process of hæmolysis and for this reason may present opportunities for its study. Blood in the subarachnoid space acts as a foreign body, hence hæmolysis, and later removal of the altered blood pigments by histiocytes, is to be expected. Histiocytes may be active sometimes before hæmolysis is apparent: even the neutrophils seem capable on occasion of engulfing the erythrocytes (Froin, 1904). For the unexpected contingency of a subarachnoid hæmorrhage one does not need to postulate the elaboration of a hæmolysin, although its employment by the organism as a means of coping with a large hæmorrhage is not an impossibility. Once the delicately adjusted erythrocytes leave the security of their normal environment of the plasma and are cut off from their normal source of oxygen, their inherent instability is increased: swelling and stromatolysis take place, the normal process of wear and tear being accelerated. The physico-chemical basis of hæmolysis is a complicated one and in subarachnoid hæmorrhage may have to do with the permeability of the erythrocyte's membrane to inorganic anions and cations, or perhaps with an impairment of its natural ability to expel sodium.

Hæmolysis is usually maximal about the fifth day. Because the hæmolytic process and the catabolism of the liberated hæmoglobin are going on continuously, spectrometry and bilirubin estimations are of little value, although interesting results were reported by Symonds (1923). Bilirubin appears early in the process of hæmolysis, sometimes within twenty-four hours of the onset of the hæmorrhage.

The length of time the products of hæmolysis persist in the subarachnoid space depends upon the amount of bleeding which has taken place, the presence of any hæmatoma (particularly in the ventricles) the briskness of the histiocytic response and the efficacy of the circulation of the fluid. It depends, too, upon the diluting effect of any therapeutic lumbar punctures. If the hæmorrhage is small

discoloration will have vanished within about sixteen days, but more often it lasts for twenty-eight days or more. The average in the series of cases reported by Richardson and Hyland (1941) was twenty days, the longest being thirty-nine days. If the bleeding has been of any size a raised protein may persist in the lumbar sac for longer than this.

For the surgeon who is visualizing the aneurysm prior to his attack, the duration of the bleeding is of some importance. Lindsay (1950) has implied that bleeding is often slight and more in the nature of an ooze. Certainly the descriptions given by recovered patients of a "sudden snap in the head" and of "a feeling of cold water rushing down the neck" are hardly consistent with an ooze, but perhaps these abnormal sensations are exaggerated in the sensorium. A consideration of the erythrocyte count, the leucocyte count, the differential count and the protein content may repay study. If the leucocytes and erythrocytes are in normal blood proportions one may assume that the hæmorrhage is active, or at any rate very recent. On about the third to fifth day the neutrophil count will fall and the lymphocyte count will rise. The lymphocytosis is absolute as well as relative and is a reactive phenomenon, which may persist for up to four weeks (Richardson and Hyland, 1941). Essick (1920) found lymphocytes and macrophages, derived from the mesothelial cells of the arachnoid, in the fluid as early as the second twenty-four hours, while Hammes (1944) found histological evidence of a commencing reaction within two hours of the bleeding. The lymphocytic response is, however, a variable factor and this variability may depend, in part, upon the degree of distension of the subarachnoid space. The neutrophils disappear because they are absorbed in the clots and because they are engaged in phagocytosis. The leucocyte count may exceed the calculated figure of one cell for every 500 erythrocytes if, as is often the case, there is an associated blood leucocytosis, and also if there has been any degree of hæmolysis.

Jackson (1949) found experimentally that the agent in blood which caused the greatest meningeal response was the hæm component: she believed it was probably bilirubin, as Bagley (1929) suggested. Hæmolysed erythrocytes, which contain free hæmoglobin, caused a greater cellular response than fresh whole blood but considerably less than degenerated blood or oxyhæmoglobin. Occasionally one may get an unexpected leucocytosis in the cerebrospinal fluid which may raise the suspicion of a meningitis.

Of greater value than the white-cell count is the protein content of the fluid. Alajouanine, Thurel and Durupt (1946) pointed out that the proteins might diffuse into the circulating fluid while the cellular elements of the blood were trapped in a clot in the depth of a sulcus. If, therefore, the amount of protein found is greater than the amount expected by reason of the lumbar erythrocyte count, one may deduce either that the protein was raised before the incident or that a hæmatoma is also present. It is generally accepted that an erythrocyte count of 1,000 per c.mm. will account for 1 mg. of protein per 100 ml. Swamy and Subramaniam (1951) give rather higher values, i.e. 10,000 R.B.C. accounting for 15 mg. If, therefore, the protein content is 140 mg. and the erythrocyte count is 100,000 one can deduce that the cerebrospinal protein was in normal amount before the bleeding and also that there is no appreciable hæmatoma. But if the protein is 140 mg. and the erythrocyte count is 15,000 one would assume that the protein was raised before the bleeding or that there is a sizeable hæmatoma present. Of course, these observations are of value only if the fluid is obtained within a few hours of the bleeding. If the withdrawal of fluid is delayed until the fourth or fifth day considerable hæmolysis may have occurred and the protein content will then be disproportionately high. After the first puncture, however, there is introduced the complicating factor of the dilution of the protein in the lumbar pool.

Because, in general, a higher proportion of blood is to be expected in the lumbar sac than in the ventricles, attempts at calculating the amount of bleeding which has taken place are apt to be fallacious. Especially is this so if a clot has formed in a sulcus or in a horn of a ventricle. If the erythrocytes are evenly dispersed and there is no hold-up a bleeding of 3 ml. should—as Lindsay (1950) has shown—give a count of 100,000 per cmm. Indeed, on purely theoretical grounds he has estimated the volume, duration and velocity of the bleeding and also the radius of the rupture in the wall of the aneurysm. Perhaps his most valuable deduction is that the withdrawal of fluid by lumbar puncture in a bleeding patient is not fraught with that danger which is sometimes attributed to it. If, over a period of one minute, sufficient fluid is removed to lower the pressure by 100 mm. it carries the same risk as a rise of 7·3 mm. in the systolic pressure spread over the same period of time. Much more dangerous than the withdrawal of fluid, therefore, are the acts of coughing, straining, or struggling, or the pain of administering a local anæsthetic.

A clear and colourless fluid does not exclude a diagnosis of spontaneous subarachnoid hæmorrhage. Martin (1931) referred to a case where the cerebrospinal fluid was free from blood on the fifth day, while a case reported by Cookson (1933) produced a clear fluid but, on counting, there were 500 erythrocytes, which is about the limit of visibility.

The finding of blood-stained fluid is less constantly met with in true intracerebral hæmorrhage (about 70% of cases), while it is distinctly rare in cerebral thrombosis.

Finally, one must recall the fact that a spontaneous subarachnoid hæmorrhage does not always betoken disease in the brain; the cause may be low down in the cord itself, sometimes without obvious localizing symptoms. Most often the cause is a vascular anomaly of the cord, but recently Fincher (1951) has collected cases of hæmorrhage in association with intradural tumours of the lumbar sac.

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Section of General Practice

President—A. TALBOT ROGERS, M.B.

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DISCUSSION ON THE INFERTILE MARRIAGE IN GENERAL PRACTICE

Dr. John C. T. Sanctuary: The cases on which this paper is based are not large in number, which is almost inevitable in a series presented by a general practitioner, the very width of the field his work covers preventing a large number of cases in any one particular class.

There are no dramatic disclosures to make; such information as I have to give may encourage the general practitioner to consider the treatment of the infertile as being in the early stages a matter for him rather than the specialist. There is no reason why a substantial proportion should ever need any investigation or advice that the family doctor is unable to give.

Man has been interested in the subject of fertility from time immemorial; prehistoric remains and early writings prove this, and the deity of fertility appears under different titles in polytheistic religions. Only within living memory, however, has real progress been made, and knowledge on the subject acquired by investigation. Unfortunately, prejudice against any subject associated with sex still exists among certain sections of the community, which tends to hamper the search for knowledge in this field. This is still far from complete, and the statement "There is a certain occult and secret species of barrenness that cannot be attributed to any cause at all" still holds good, though it was made by Nicholas Culpeper in 1652 in his book *English Physician and Family Dispensatory*.

There is among general practitioners a tendency to consider the treatment of a childless couple as being outside the family doctor's scope and to refer these patients for advice elsewhere at once, quite irrespective of whether the consultant whose advice is sought has a specific interest in this subject.

This attitude on the part of the doctor is due to two basic causes. Firstly, the absence of any teaching on the subject in the already crowded curriculum of the medical schools, and secondly, the hesitation of the patient to consult the youthful practitioner on subjects of great personal intimacy, particularly if the doctor is unmarried. By the time the doctor has acquired the desirable appearance of benevolent middle age together with the capacity for himself feeling unembarrassed when discussing the more intimate sexual matters, he is inclined to pass into other hands matters in which he has had little consulting experience. By doing so he is shirking his duty and avoiding his obligations to both his colleagues and patients.

The family doctor has a very real responsibility for undertaking this work, saving the patient mental and physical stress and releasing the infertilologist for the cases that really need his advice. During the 10 years up to October, 1953, I have collected a series of 203 successive cases in my consulting room.

Although subfertility may be the responsibility of either partner of the marriage, it is the wife who comes to consult the doctor while the husband may arrive to lend moral support. He is usually quite surprised to find that he may not be fertile although he is potent, and that potency and fertility are dissociated.

As the result of successful treatment is conception by the wife, it is inevitable that the doctor regards her as the basic factor in the case, although she may not be responsible for her failure to conceive.

The series of cases are divided into three groups in order to demonstrate the principles which I have mentioned.

(A) Those who have had no investigation or treatment other than those obtainable in the consulting room of a general practitioner.

(B) Those who required further investigation which should be available to the doctor, if he cannot himself undertake it, but with whose treatment he can then continue.

(C) Those who needed further specialist investigation and treatment.

Analysed in this way, the total figures read as follows:

Category	(A) G.P. only	(B) G.P. plus investigation	(C) Specialist	Total
	89	65	49	203

Dividing these into success and failure categories, we have:

Category	Conceived (A)	(B)	(C)	Failed (A)	(B)	(C)
	60	32	11	29	33	38

Considering these figures, the first thing that seems apparent is that all failures under (A) ought to have been investigated, and those under (B) ought to have been referred to a specialist.

The fact that this was not always done is explained by (1) The non-return of the patients; (2) Hopeless subfertility amounting to inevitable sterility; (3) The decision of the patients not to pursue the matter further. A number will not consider going as far as accepting operative treatment which can never be put forward as more than hopeful.

I would stress that these figures are not being put forward for comparison with those published by expert infertilologists and high-grade subfertility clinics. It is impossible to say to what extent the patients who consult their family doctor and those seen by the consultant are the same, and the advantage of being able to claim credit for the simple cases will rest with the former.

The age at which advice is first sought by the infertile couple is a matter of some interest. Unfortunately I have no records covering the series as far as the husband is concerned. As to the age of the wife, I have divided the series into five-year groups, giving her age on the date on which she first consulted me on account of her subfertility.

TABLE I

Table of Age Groups	Number of Cases
Under 20	7
20–24	31
25–29	73
30–34	58
35–39	28
40 and over	6
	203

In Table I the majority of cases are in the late twenties or early thirties where one would naturally expect to find them; at the extremes one finds a few impatient enthusiasts under 20, and a very similar number of hopefuls over 40.

Advice is usually sought after from two to five years of subfertility, though I have known the period to vary from a very few months to over 17 years. One patient came after 15 years of married life, saying that her husband had suddenly informed her that as she had failed to give him a child he intended to go off with another woman unless the wife conceived without further delay. On investigation the wife proved to be perfectly normal, and the husband had a complete azospermia, which I have to admit gave me some mental satisfaction. They are still together.

It has been my general plan in cases where the wife is under 35 years of age on the occasion of her first examination not to press the investigation further immediately if I have found no apparent abnormality or suggestion thereof.

In these cases general principles are laid down as to fertile dates, frequency of intercourse and routine treatment for trying to improve fertility and nidation in the prospective parents. I usually recommend the couple to try this approach for about three months and return if unsuccessful.

The fact that 60 cases out of 167 where the wife was under 35 years of age responded to this approach, encourages me to consider that it is a wholly proper manner in which to commence the treatment.

In patients over 35 years of age there is not only less time to spare and more likelihood of a pathological subfertility, but there is usually a longer period of disappointment behind them. They both need and seek immediate investigation, and with them, and with those who have failed in the first group after what may be called the primary advice and treatment, it becomes necessary to go on to the next step in investigation.

The main points in this stage are:

(1) Post-coital tests.
(2) Calculation of the time of ovulation by temperature charts.
(3) Hysterosalpingography.
(4) Seminology.

Items 1 and 2 are within the scope of the practitioner who cares to undertake them, and some of us may be fortunate enough to be able to deal with our own hysterosalpingography; if not, it depends on how co-operative the nearest department where this work is undertaken proves to be.

Seminology is, however, a very different and highly specialized matter, and requires the opinion of a first-class seminologist. The pathological laboratory that sends a report stating "Large numbers of highly motile spermatozoa"—and I have seen reports that do this—is an insult to the practitioner, who could easily find that out for himself. It is little more useful than a blood report would be that stated "Large numbers of red blood cells".

It is essential for the practitioner to have before him a properly analysed report, with the opinion of the seminologist as to whether the subject is fertile, and if not, what hope there is of his becoming so spontaneously, or of responding to treatment.

My own remarks on investigation I shall confine to a description of the use of temperature charts to determine the time of ovulation and to the information obtained from hysterosalpingography. The usefulness of seminological reports is demonstrated by Table II.

TABLE II.—SEMINOLOGICAL REPORT

Male		Female		Conception: Succeeded	Conception: Failed
Normal		(*a*) Fertile	4	2	2
Fertile	22	(*b*) Subfertile	18	6	12
Borderline	3	(*a*) Fertile	1	1	0
		(*b*) Subfertile	2	0	2
Subfertile	14	(*a*) Fertile	9	2	7
		(*b*) Subfertile	3	1	2
		(*c*) Unknown	2	0	2
Total	39		39	12	27

In commenting on the above it would be dangerous to draw any major conclusions from such a small list, but there are one or two interesting points. In the first class there are two cases where there was no apparent cause for sterility in either partner as revealed by exhaustive investigation, but the marriage remained sterile. In all the others such success as there was followed treatment of one or both partners, and in only three cases where the male was reported as subfertile on the first occasion did conception occur at a later date. This supports the generally accepted opinion on the difficulty of treating the subfertile male. I have only included those seminological investigations which I consider reliable and have left out a number of earlier investigations.

Post-coital tests.—The practitioner who possesses a microscope can learn to do useful post-coital tests quite easily, and if not satisfied with the results can get them checked by an expert.

Temperature charts.—The use of these is based on the principle that at the time of ovulation the temperature rises two- or three-fifths of a degree and does not fall again until the onset of the next period. Charts, originally designed by Pendleton Tompkins of Philadelphia are available, together with full instructions on how to take the rectal temperature and record it, and a sample chart for each patient. I have found no difficulty in getting the patients to keep these accurately.

Hysterosalpingography.—It is ordinarily outside the field of the practitioner, but with proper co-operation there is no reason why the results of the investigations should not be made available to him.

My own results from this series of cases are as follows (Table III):

TABLE III

Salpingographies Performed

Normal Results	Abnormal	Total
32	54	86

Abnormality	Conceived	Failed	Total
Anatomy of uterus ..	1	2	3
Tubal obstructions:			
One Tube	5	6	11
Both Tubes ..	10	30	40
	16	38	54

In cases with one tube obstructed or missing, the prospects are affected by the ovulating ovary. If this is on the side from which the tube is not functioning they are obviously not so good as if the ovary on the normal side is ovulating.

Cases with obstruction of both tubes at the time of salpingography show a 25% success under treatment, and as there are frequently other causes to be considered, I do not think this altogether unsatisfactory. It does point to the fact that a number of these cases must be due to temporary tubal spasm on which the injection of iodized oil has a therapeutic effect.

Finally, there are the 49 cases which were referred to specialists as being beyond the scope of a general practitioner.

The fact that 11 of these conceived under treatment leads me to regret that, owing to their own unwillingness, more of the failures did not find their way to specialists.

Table IV shows the analysis of success and failure from all causes and the success and failure rates. Some of the causes of subfertility in the cases which were successful without full investigation must be based on circumstantial evidence, notably those under (4). The unknown causes of subfertility are also too large in number, but, with few exceptions, are due to the patients declining to carry the matter further or simply failing to return.

TABLE IV
Analysis of Success and Failure. Primary Causes

Cause of Subfertility	Conceived	Failed, or result unknown	Total
1. Dyspareunia	8	0	8
2. Endometriosis	1	2	3
3. Infective conditions	12	1	13
4. Nidatory and defective timing problems	33	4	37
5. Ovulatory abnormalities	18	12	30
6. Tubal obstruction	15	33	48
7. Anatomical uterine abnormalities	1	2	3
8. Uterine tuberculosis	0	2	2
9. Male impotence	5	1	6
10. Defective semen	5	16	21
11. Unknown	5	27	32
	103	100	203

Table IV shows what, at first glance, might be taken to mean a disagreement with some of the earlier figures. This occurs because in certain cases two possible causes have tended to be present, in which case I have quoted the more important or primary cause. It is interesting to note the high fertility rate among impotent men; the only one of these given as a failure refused to co-operate in any form of attempt to transfer his semen to his wife.

SUMMARY

I have endeavoured in this paper to present the main points of interest and importance and to avoid multiple tables of unimportant statistics. My object has been to urge that the treatment of the Infertile Marriage comes largely within the scope of the family doctor. Success is very flattering as it produces most grateful patients with a quite disproportionate opinion of one's ability. Incidents occur which appeal to one's sense of humour. A wife came to see me asserting that she was sure she must be pregnant because, though she felt quite normal, her husband was being sick every morning. Investigation proved her diagnosis to be correct.

Establishing the date of conception in another patient, not one of this or any subfertility series, led me to suggest that she might have conceived on a certain date. She replied that possibly I might be right, but as she and her husband had intercourse every night except during her period, it was hard to say. It was, moreover, the first month since their marriage two years earlier that they had not used contraceptives. I was lost in admiration at the potency and fertility of the husband who could ejaculate sperms daily and which, after two years, proved of sufficient maturity to fertilize his wife. I mention this case to show the extremes of fertility which one can meet.

In conclusion I may add that since I worked out the figures for this paper, at least three of those mentioned as failures have conceived and could be moved from the debit to the credit side. Of these, one was a case for whom we could find no reason for her failure to conceive, and she emigrated to South Africa. I have just heard that she is expecting to be confined in a few days.

The second is a case whose salpingogram showed a partial filling of both tubes.

In the third case the right tube was removed some years ago, and she had an obstruction at the fimbrial end of her left tube. She was operated on last December, and it was found that she was ovulating from the right ovary. This ovary was removed, thus forcing her to ovulate from the left and the tube was insufflated from the abdominal end. Following this she saw only one further period and is now about nine weeks pregnant.

Mr. D. Maxwell: As Dr. Sanctuary has rightly said, many cases of infertility should never get into the consultant's hands.

It may now be asked what the consultant can offer the wife which the practitioner cannot give:

(1) *Detailed opinion on the pelvis*, if necessary under anæsthesia, including endometrial biopsy with possible revelation of hypoplasia, anovulation, and tuberculosis in particular.

(2) *Investigation of the cervix* in co-operation with the pathologist—pH, cellular and bacterial content of the cervical plug, degree of stickiness of the cervical mucus. Cauterization for endocervicitis and erosion.

(3) *Investigation of tubal patency*—insufflation and/or salpingography. Rubin states that 36% of his private patients became pregnant within three months of one or two CO_2 insufflations.

(4) *Operative procedures*—hymenectomy; uterine suspensions; myomectomy; plastic procedures for rare congenital abnormalities of the uterus; salpingostomy; tubal inplantation; operations on the cervix.

(5) *Artificial insemination.*

My intention is to select only a few points out of these five headings, some of which are of interest to the practitioner.

Anovulation.—There may or may not be evidence of hypoplasia in such cases, but frequently there is dysmenorrhœa or amenorrhœa.

Diagnosis is usually possible by temperature charts and endometrial biopsy which should show *absence* of luteinization and tortuous glands in the premenstrual phase.

Treatment if under 25 is probably most effective by giving minimal doses of X-rays according to the technique advised by the late Carter Braine. All radiotherapists are not agreed about the action of X-rays in these cases and will not always co-operate, but my own personal experience with numerous cases I have referred to Carter Braine for many years in the past has been most favourable.

After 25, hormonal treatment is rather problematic and difficult to keep up, but comprises essentially large doses of œstrogens, then stopping these to get a withdrawal bleeding and then administering gonadotrophins.

Tuberculosis (endometrial).—Sharman in Glasgow in 1943 showed that 5·1% of his subfertility cases showed unsuspected tuberculosis, but has lowered this incidence considerably in the last few years. Stallworthy of Oxford and Magnus Haines, pathologist at the Chelsea Hospital for Women, stressed the importance of this disease in cases of failure of conception. Endometrial tuberculosis is 10 to 15 times as common in sterile women than in those who are not. 83% of Sharman's cases of tuberculous endometritis showed tubal blockage.

Treatment of endometrial tuberculosis consists in giving streptomycin and PAS—to this might be added sanatorium regime and good diet and vitamins.

The Cervix

This is at fault in the opinion of many authorities in about 30% of all cases.

pH.—The Americans and a diminishing number of authorities in this country consider that pH estimations are of value. That of the cervix should run between 7 and 8 and of the vagina between 4 and 5. Suitable Nitrazene test papers like litmus paper are obtainable in the U.S.A. for this purpose. It is questionable as to what can be done if the pH of the cervix is found to be abnormal. Certain French firms claim that large doses of progestogens can alter the pH of the cervix. On a few occasions only have I found the pH abnormal, and most teaching authorities in London have given up this practice.

Bacterial content.—The cervical cascade or plug, at the time of ovulation at any rate, should be crystal clear in a healthy woman; if not, a drop on a slide will usually show a high cellular content and a swab given to a bacteriologist will frequently grow organisms. Dame Hilda Lloyd of Birmingham published a paper prior to 1950 showing the good effects of sulfa drugs and œstrogens in these patients.

The dry cervix.—Recently much attention has been brought to this point, particularly by Dr. H. A. Davidson, Mr. R. Christie Brown, Miss Mary Barton and Dr. B. P. Wiesner. Anyone who does post-coital tests will immediately recognize the condition and frequently without the microscope. One might ask—how can a salmon leap up a waterfall if there is little or no water running? Green-Armytage has stressed the importance of orgasm in subfertile women, as probably this results in a flushing out of the cervical canal and clearing the way for the sperms.

As regards treatment, most authorities advise œstrogens in small doses for the 10 days following each period during the œstrin phases, usually for several months. Much work has been done comparatively recently by Clift on the character of the cervical secretion. This can be measured, and alters very markedly as soon as the patient is pregnant. In fact, Clift can diagnose pregnancy by estimating the elasticity of the cervical mucus. If it is very adhesive, œstrogens will improve this. For the infected cervix the doctor should be advised by the bacteriologist what to give, depending on the sensitivity of the organism found. Gross endocervicitis and erosion should be treated by the cautery and not touched again for a period of at least six weeks. This does not hurt in 90% of women. Bethel Solomons of Dublin has stressed the importance of never coning the cervix in subfertile patients.

Tubal Factor

Both tubes were occluded in 15% of cases and 66% of tubes were patent in 1,190 cases of primary sterility investigated by Green-Armytage. 21·6% of tubes were apparently blocked in Stallworthy's 1947 series, but he was able to reduce these to 12·8% using spasmolytics. My own figures concur both privately and in hospital with Green-Armytage as regards therapeutic success following salpingography, namely 40%. Both salpingography and insufflation can be done without anæsthesia in the majority of cases, and should be accompanied by the administration of an anti-spasmodic such as atropine or octyl nitrite. They are both best performed about 72 hours after menstruation has finished. The advantage of the oil test is that a definite film can be taken and the fate of the oil determined later, also the site of any block can be demonstrated. The disadvantage, according to Rubin, is that adhesions within the tube or at the fimbriated end may result.

The advantages of insufflation include the comparative ease with which it can be done in the consulting room in many cases, the eliciting of shoulder pain—possibly the most conclusive proof of all that there is tubal patency. In addition, no anæsthetic or X-ray machine or radiologist is necessary, thus saving expense. A permanent record in the form of a kymograph tracing can be filed.

Operative Procedures

I see many cases yearly who are referred for hymenectomy and should never be referred. Many cases of impossible, difficult or incomplete intercourse can be treated by vaginal dilators—if the patient can be instructed how to use graduated ones following the evening hot bath.

Suspension operations for retroversion have a reserved and small place unless there is dyspareunia from an associated prolapsed ovary. The supposed "kinked hose" theory which is possibly related to retroversion is a doubtful one—as we see so many cases of retroversion who become pregnant easily.

Myomectomy undoubtedly has a place, especially if there is a reasonable sized submucous fibroid confirmed by salpingography.

Salpingostomy and Tubal Implantation.—Even in very expert hands, if the lesion is bilateral the chance of success is about 18% according to Bonney, Read and Green-Armytage's figures. In the hands of Green-Armytage of London and Palmer of Paris, 30% success is claimed with tubo-uterine implantations.

Artificial Insemination

Donors' Sperms.—I have decided many years ago on the advice of Aleck Bourne to have nothing to do with this as I cannot see morally how the sperms can be obtained without breaking at least one of the Commandments.

Husbands' Sperms.—It must be up to Dr. Davidson or one of his genito-urinary colleagues to decide sometimes when this is necessary, but in experienced hands it has perhaps only 10% success, but certain authorities would question this figure. Until we have more accurate tests for the exact time of ovulation, such as the Farris test on rats, there is likely to continue to be a poor figure, but this is not so in Philadelphia, where Douglas Murphy claims 80% success with donors' sperms provided only that the wife is 100%.

A single insemination produced 40% of the conceptions.

It required only three inseminations to bring about 76% of the conceptions.

Prevention of Early Miscarriage

Very many cases conceive, but possibly miscarry very early, and the work of Christie Brown (1951, 1952) is too well known for me to elaborate.

Nevertheless, I would stress the very great importance of using his methods and fertilizing the soil before the seed is sown. Results are best obtained by using a dose of ethisterone 10 mg. and ethinyl œstradiol 0·01 mg. in the form of Orasecron of Schering or Amenerone of Roussel from the twelfth day of the cycle until the next bleeding or eighteenth week of the pregnancy if the patient conceives. In addition, the insertion of a progesterone implant will sometimes be indicated, as soon as a hormone test is positive. Six pellets of 25 mg. are recommended and are inserted under local anæsthesia under the fascia covering the gluteus maximus immediately below the iliac crest—using a trocar and cannula.

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Dr. H. A. Davidson: Dr. Sanctuary has expressed the hope that he might encourage the general practitioner to consider the treatment of the childless couple as very much a matter for him, and I should like to add my hopes to his. It is precisely the width of the G.P.'s field which makes it possible for him to be of real help; for there are at least three specialities involved in approaching a fertility problem, and the general practitioner is the most likely person to keep in mind that it needs more than only a fertile woman, or only a fertile man, or only a psychoanalysis, to produce a child.

The Post-coital Test

The first requirement for fertilization is that spermatozoa should reach the cervix in adequate numbers, and that they should find conditions enabling them to survive, and to proceed on their journey towards the ovum. Therefore the first step in the clinical investigation of a childless woman should be to look for spermatozoa in the cervical secretions after coitus, i.e., the post-coital test. For until we have found a dense and active sperm population in the cervix conception is unlikely, no matter how favourable the gynæcologist's and seminologist's individual verdicts.

The post-coital test is simple, brief, and painless. The woman is instructed to attend near her presumed ovulation time, and intercourse should have taken place 7 to 12 hours previously. The cervix is exposed with a bivalve speculum and the contents of the cervical canal aspirated. The mucus is examined immediately under the microscope.

There are two items of information we look for in the test: firstly, the quality of the cervical mucus itself, and, secondly, the denseness and quality of its sperm population. Cervical mucus at ovulation time should be copious and clear, and it can be drawn out into a thin thread. It is easy to recognize if we remember that its consistence is similar to that of fresh egg white. Any sample showing opalescence or greater viscosity is likely to be unfavourable for spermatozoa. The sperm population in a good post-coital result is as dense as in fresh semen, with masses of progressively motile spermatozoa. Four to five progressing spermatozoa per high-power field can be regarded as a fair result, and anything poorer than this calls for further investigation.

Interpretation of post-coital findings.—A good post-coital result means that all is well up to the level of the cervical canal. If there is no conception within a very few months after such findings we must assume that there is some fault above this level and ask the gynæcologist to investigate further. A poor post-coital result means that either the semen is poor, or the cervical secretions unfavourable, or else that intercourse is inadequate mechanically, so that the semen is not deposited near the cervical mucus. The next step in such a case must be a direct semen test for the husband. If the semen report is favourable it will not be difficult to find out whether the poor post-coital result is due to poor cervical secretions or inadequate deposition of semen. If, on the other hand, the husband is found to be subfertile, his condition should be rectified, meanwhile limiting the wife's investigation to the exclusion of gross abnormalities.

Here I shall leave the no-man's-land of post-coital tests and come to my own subject, that of male fertility.

Male Fertility

Disturbances of fertility in the male are as common as in the female. One of the reasons, perhaps, why we still fail to realize this is the confusion between male sexual potency and fertility. These two factors bear very little relation to each other, and we find at least as many sexually potent subfertile men as we find impotent men who produce excellent semen. If we remember this fact, and explain it to our male patients, much of their reluctance to submit to semen examination will disappear.

Semen analysis.—The beginning and the end, literally, of the husband's investigation is the semen test. Hence it is vitally important that this is conducted in a way likely to give reliable and reproducible results. It may appear unnecessary to stress this; yet the fact remains that few laboratories have the facilities, the trained personnel, or even the time, to deal with this work so that errors in diagnosis are distressingly common.

There is no time to go into the details of semen examination here, and I would refer those who are interested to the fairly extensive literature on the subject. For the present, I will state only the *sine qua non* of a semen report.

(1) The specimen should be collected directly into a warmed glass container either by masturbation or coitus interruptus. Specimens collected in rubber sheaths are useless for a complete semen examination since the rubber kills spermatozoa.

(2) The abstinence preceding the test should be stated on the report. If it is less than two full days, the specimen may not be representative of the man's average level.

(3) Semen should not be older than two hours when it is examined. Any delay beyond this makes the motility findings unreliable. Therefore the age of the specimen should also be given on the report.

(4) We need at least the following four items of information: The semen volume, the sperm density, the percentage motility, and the percentage of morphologically abnormal spermatozoa. Omission of any one of these may invalidate the whole report.

(5) Finally, the pathologist should append his verdict as to whether he considers the semen to be normally fertile or otherwise. This is necessary, since methods of examination vary in different laboratories, and therefore standards also differ.

Unfortunately, I can confirm Dr. Sanctuary's experience of seeing semen reports stating just that "spermatozoa were present and motile", without any further details. This, of course, is worse than useless, since it takes us no farther, but at the same time creates the illusion that we have done our duty by the patient.

Whenever we receive an unfavourable verdict on a man's semen we must consider the possibility of a temporary disturbance. Unless clinical examination has already led us to expect poor semen we should always insist upon a check test two to four weeks later.

Interpretation of semen reports.—The pathologist may give us three types of reports. Firstly, the semen may show normal findings; secondly, there may be no spermatozoa present; or, finally, he may report a deficiency in the volume of semen, the numbers, morphology, or motility of the spermatozoa, or several of these together.

Normal semen: As I mentioned before, standards vary from one worker to the other, but there is fairly general agreement that normal semen shows a volume of 1·5 c.c. or more, and contains 40 or more million spermatozoa per c.c., of which at least 60% should be normal morphologically, and 40% or more should be progressively motile. Of course, there are men whose wives conceive easily with semen below this standard, and it is well to keep in mind the difference between subfertility and complete sterility.

Azoospermia: Here we need to know whether this is due to failure of spermatogenesis, or to an obstruction. The answer is provided by testicular biopsy. If the biopsy section shows no spermatogenesis the case is usually hopeless. If, on the other hand, spermatozoa are present, we know that there is an obstruction in the efferent system, and surgery may be able to overcome this.

Other semen defects: These include impairment of volume, sperm density, morphology or motility. Very commonly several of these are found together, and if we say that a man is suffering from oligozoospermia, or from any other one defect, it means that we have selected the most prominent fault, not that we have classified the patient for diagnostic or therapeutic purposes.

Diagnosis and Treatment

A semen report is not a diagnosis. It may tell us that something is at fault, but it does not tell us why. The "why", i.e. the full diagnosis which we need in order to assess prognosis and treatment, can only be provided by a history and physical examination. Needless to say, it is impossible to consider treatment on the basis of a semen report alone.

The time available does not permit a complete survey of the causes and treatment of male subfertility. Also, such detail would be beyond the scope of our present subject, for many cases would have to be referred to the specialist. Therefore I have decided to restrict myself as much as possible to common conditions, and to matters of immediate practical application.

For completeness' sake, we must list the causes of impaired fertility as constitutional, endocrine, dietetic, occupational, traumatic, and infectious. Of these, two have acquired quite unmerited prominence, and it may be useful to try and see them in their proper perspective.

Endocrines: There is a widespread tendency to regard problems of male subfertility as mainly the endocrinologist's province. Yet the more we learn of the subject, the less we find that this is the case, and it is beginning to look as if hormone deficiencies are no more common in this field than in any other branch of medicine. It is true that now and again we meet a genuine case of hypogonadism, or hypopituitarism, or hypothyroidism, but the majority of subfertile men show no signs of endocrine deficiency. Hence it is not surprising that hormone treatment has given disappointing results. Unfortunately, there is more to it than absence of improvement, since in many cases unnecessary hormone administration depresses fertility. The commonest offender is testosterone, despite the fact that many workers have pointed out its depressant effect on spermatogenesis. It cannot be repeated too often that testosterone has only a very limited application in the treatment of semen defects, and its administration is unjustifiable in the absence of clinical signs of androgen deficiency.

Vitamins and diet: Fortunately, vitamins do not depress male fertility; but their administration in patients showing no signs of vitamin deficiency is wasteful and delays a correct assessment of the situation. There is no evidence that under civilized conditions a diet can be so low in the relevant vitamins as to cause subfertility, nor does smoking or drinking affect sperm production.

Leaving these uncommon causes of semen deficiencies, in the hope that they will eventually find their proper place, I will proceed to the more common findings.

Mumps: It is not uncommon for adolescents and adults to develop mumps-orchitis following the parotid swelling. Occasionally orchitis alone occurs, without parotitis. This is a grave danger to fertility, and bilateral orchitis may lead to complete and incurable sterility. It is vitally important, therefore, to try every possible means of preventing such a complication, and treatment is of the utmost urgency when it threatens. Fortunately some of the new antibiotics seem to be effective against the infection, and we may hope to see fewer of its victims in future. There is no convincing evidence that mumps in children affects the testes.

Undescended testes: This is another cause of male subfertility where our only hope lies in the general practitioner. If today we still see men who are sterile because of undescended testes or

subfertile because of incomplete descent, this is a tragedy which we might have prevented. The treatment of undescended, incompletely descended, or maldescended testes is a matter of urgency if the patient is to be fertile. Time is limited, for treatment at, or shortly before, adolescence may be too late. Therefore every boy suffering from this condition should be referred to the urologist as soon as it is diagnosed, and the decision of whether treatment should be delayed or not, and what form it is to take, is best left to him.

Disturbances of testicular temperature regulation: This is probably the commonest cause of semen deficiency, and in my opinion well over half the patients I see fall into this group. The testes cannot work at body temperature, but are maintained at about 2° C. below this by movements of the scrotum and cremaster muscles. This is the reason why in warm weather the testes hang low, moving away from the body and its radiation. Conversely, when their temperature becomes too low, the scrotum contracts, bringing them close to the body and forming a thicker covering.

It has been proved by animal experiments that if the testes are kept at body temperature, spermatogenesis ceases and sterility results. Probably this is the reason why cryptorchids are sterile. Lesser increases in the average testicular temperature can still result in serious disturbances of fertility.

It is interesting to note that short exposure to comparatively high temperatures, such as hot baths, have no deleterious effects; it is the prolonged slight increase above the optimum level which seems to be most harmful.

The many cases of male subfertility caused by disturbance of testicular temperature regulation fall under three main headings: scrotal supports, varicoceles, and minor degrees of incomplete descent of the testes. Two of these we can usually cure, and one we can prevent.

(1) Scrotal supports. These abolish movements of the testes and keep them close to the body. Also, they prevent heat loss by radiation and evaporation of sweat. The increasing fashion of wearing "jockey type" underwear is making this quite a serious problem. Within the last six months I have seen two cases of oligozoospermia who had been given up as hopeless because endocrine treatment had failed, and who produced normal semen within three months of abandoning their scrotal supports, without any other treatment than cold sponging of the scrotum.

(2) Varicoceles. Varicose veins are like a radiator at blood heat. If the testes move away from the body in order to lose heat the varicocele follows them and keeps up their temperature.

I have now the returns of the first 14 cases of a very much larger series of varicocele operations. Most of these were " hopeless " cases of oligozoospermia. So far 12 have improved and there have been seven pregnancies within six months of operation. The two who failed to improve still have varicoceles and await a second operation. This series will be published eventually.

It follows from the above that we must reconsider our attitude towards varicoceles. We cannot afford to continue disregarding them, and if we advise our varicocele cases to wear a support we may inadvertently sterilize them.

It is true that many men who have varicoceles, and who wear scrotal supports, are adequately fertile. The explanation is probably that some men are gifted with very high fertility and can suffer considerable damage without falling below normal limits.

(3) Incomplete descent. Minor degrees of this are far commoner than we have thought hitherto. In these cases the short spermatic cords make it impossible for the testes to hang sufficiently low to cool down. On examination in a warm room the appearance is characteristic: we see an empty fold of scrotum hanging down below the testes. Usually the patient recalls occasions when the testes slip into the inguinal region. It is important, therefore, to pay attention to any, even minor, faults of testicular descent in boys and young men, and to have them attended to in time.

Mr. Reynold H. Boyd: The infertile marriage is a sizeable problem—there are 450,000 marriages a year, of which some 7% or more are infertile, thus adding 30,000 couples annually to the pool requiring advice or investigation. By various means and treatment one-third of these become fertile. It is important that the other two-thirds should not be turned into nervous wrecks. In no field of medicine is the patient's doctor of more importance, and he should retain an active and overriding influence lest the "best years of their lives" are spent going from clinic to clinic. Procreation is not the sole purpose of marriage and, above all, a happy marriage should be maintained.

In a number of cases imperforate hymen is the cause, and few of these need stay long undiagnosed or, indeed, ever come to a clinic. A recent exception to this was that of a woman who had been married 6½ years and in whom the vaginal orifice was found to be blocked by a pedunculated fibromyoma arising from the urethral meatus.

Not a few patients are found to have been acting on misconstrued advice—the usual error being to concentrate intercourse on the 14th day *after the period ends* instead of on or around the 14th day *after the commencement of the period.* Many couples believe the most fertile time to be just before or just after the period. It is not necessary to attend a clinic to have these ideas corrected.

It is a great help to a clinic to have the couple's religion mentioned in the doctor's letter. The investigation of Catholic couples is different from the routine approach.

A hopeless prognosis should be given but rarely. Although in the main a density of 20,000,000 and upwards of spermatozoa per ml. is a prerequisite for fertility, I have seen pregnancies from counts as low as 500,000 per ml. But such a pregnancy is only likely to happen when the investigation has been concluded and the couple has achieved a resigned and philosophical acceptance of the facts and sometimes only after the adopting of a child.

Much can be done to prevent infertility in men by: (*a*) Early correct advice in cases of undescended testes. (*b*) Prevention and treatment of adolescent or adult mumps-orchitis by giving immune serum, stilbœstrol, and, if available, cortisone or ACTH to the declared case. (*c*) Advising an early and quick family in cases of varicocele or by recommending operation which, if carefully done, produces considerable improvement in the spermatozoa count. To ensure the best results, the spermatic artery should be tied when the veins of the pampiniform plexus are ligatured.

Little can be done for hypogonadal states, and the treatment of oligozoospermia is also unsatisfactory; although variable counts can be improved by stimulation therapy (ranging from gonadotrophins to pituitary X-radiation), *a fixed low count* must be accepted as unalterable. In such cases artificial insemination is a powerful aid and especially cap-insemination, whereby the whole volume of semen may be used with or without concentration by centrifuging. It will be possible in time, with the aid of deep freeze techniques, to make up a fertile specimen from a number of subfertile ones for use on the appropriate day.

It is unfashionable to attribute infertility to retroversion, but in many cases the cervical os is most effectively sealed by the anterior vaginal wall. Here, too, artificial insemination is successful.

Artificial insemination can also by-pass a mucous plug in the cervix. In a few cases this plug remains almost, if not completely, impenetrable even at the ovulation time.

Tubal insufflation is not only of immense diagnostic value but also the most successful single treatment of infertility in women, even when the tubes show no signs of spasm or blockage.

So far as I know there is no successful way of inducing ovulation in anovulatory cases, but for this and for other less accurately diagnosed conditions many useless and prolonged endocrine treatments are given.

And lastly, careful technique in epididymovasostomy can overcome epididymal blockage and give successful results in selected cases.

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President—C. T. Potter, M.D., F.R.C.P.

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The Problem of Blind Children and the Responsibilities of the Pædiatrician

PRESIDENTIAL ADDRESS

By C. T. Potter, M.D., F.R.C.P.

Blind children are the concern not only of the ophthalmologist or neurologist but also of the pædiatrician whose interests embrace all aspects of the problem of child health including physical and mental development. It may be of interest to know something of the changing picture over the past years—the change in the incidence of the main causes of blindness in children, as well as the change in the attitude towards those suffering from this handicap.

Although records in the past were not properly kept we get an idea of the state of affairs about 100 years ago by studying the figures of the causes of blindness in Inmates of the Liverpool School for the Indigent Blind 1791 to 1872, a period covering 83 years. Here we find that infection such as smallpox, "inflammation", "fever", and measles accounted for 823 out of 1,709 cases, i.e. about 50%, and was therefore preventable. During the succeeding years vaccination has eliminated smallpox as a cause, and no doubt better nursing and post-natal care have played a large part in reducing the large group due to "inflammation". Blindness from "fever" and measles is rarely seen today.

In 1884 the Ophthalmological Society carried out a survey and found that over 30% of those in blind schools and institutions suffered from the sequelæ of Ophthalmia Neonatorum. The incidence of this disease remained high until about 20 years ago, since when there has been a rapid diminution to an almost negligible amount.

Professor A. Sorsby has shown that during the 20-year period from 1923 to 1943 the numbers of registered blind children between 5 and 16 years in England and Wales had fallen from 2,722 to 1,355. This fall to about half the number is due largely to the reduction of the complications of infectious disease including Ophthalmia Neonatorum. The effective control of this disease may be attributed to many factors. The practice of Credé was of undoubted value; by the obligatory notification of the disease in 1914 organized treatment became possible; the advent of the sulphonamides and later antibiotics were especially beneficial both prophylactically and in treatment; and I believe, too, that credit must be given to better ante-natal care, and better nursing in the post-natal period.

Main Causes of Blindness in Children Today

The decrease in blindness due to preventable diseases was so marked that we felt we had reached a state of affairs in this country in which the causes of blindness in children were confined to a few acquired causes and to hereditary and congenital causes, which for the most part could not be prevented at our present state of knowledge. At this stage we were beginning to feel fairly optimistic about the situation but our optimism was short-lived. During the last few years two other conditions have entered the field—the sequelæ of tuberculous meningitis in children who have survived that disease, and more especially retrolental fibroplasia.

The following tables give a picture of the present situation.

Table I.—Causes of Blindness in Sunshine Homes, October 1953

Congenital	No.	Post Natal			
Optic atrophy	12				
Cataract	9	Glioma	13		
Buphthalmos	9	Optic atrophy (4)			
Rudimentary globes ..	7	„ „ cerebral tumour	1	Retrolental	
Microphthalmos	5	„ „ meningitis	1	fibroplasia	
Aniridia	4	„ „ trauma	1		
Coloboma	2	„ „ oxycephaly	1	84	
Aphakia	2				
Cortical blindness	2				
Others	11				
	63		17	84	

Total No. Cases = 164. Retrolental fibroplasia = 51·2%

Table I shows the congenital conditions which between 1941 and 1948 were the main causes of blindness in the Sunshine Homes. Conditions which occurred post-natally included glioma, a few cases of secondary optic atrophy, and retrolental fibroplasia. Out of 164 cases 63 were congenital and 101 post-natal, of which 84 were due to retrolental fibroplasia i.e. 51·2% of the total.

TABLE II.—DIAGNOSIS OF CASES INTERVIEWED AT ROYAL NATIONAL INSTITUTE FOR THE BLIND, OCTOBER 1951 TO DECEMBER 1953

Congenital	No.	Post Natal		
Cataract	20			
Optic atrophy	19	Glioma	14	
Microphthalmos	16	Optic atrophy (10)		
Buphthalmos	13	„ „ hydrocephalus	4	
Rudimentary globes	6	„ „ cerebral tumour	2	Retrolental
Cortical blindness	6	„ „ trauma	3	fibroplasia
Aniridia	4	„ „ oxycephaly	1	151
Choroid- retinal degeneration	3	T.B. meningitis	7	
		Meningitis	1	
Coloboma	2	Pseudoglioma	1	
Toxoplasmosis	2			
Others	8			
	99		33	151

Total No. Cases = 283. Retrolental fibroplasia = 53·3%

Table II includes cases interviewed between October 1951 and December 1953. They include some of the cases at present in the Sunshine Homes, some awaiting admission, and others who were mentally deficient and not eligible for admission.

The same pattern is shown in the congenital list as in Table I, and includes 2 cases of toxoplasmosis. In the post-natal cases there were, amongst others, 7 cases due to sequelæ of tuberculous meningitis, the blindness here being due to optic atrophy or some central defect. The cases following toxoplasmosis and tuberculous meningitis were mentally deficient. Of these 283 cases 151 were due to retrolental fibroplasia, i.e. 53·3%.

TABLE III.—CASES OF RETROLENTAL FIBROPLASIA INTERVIEWED AT R.N.I.B. OR IN SUNSHINE HOMES BETWEEN 1946 AND 1951

Born in 1946	5
„ 1947	12
„ 1948	21
„ 1949	47
„ 1950	44
„ 1951	48
Total	177

Table III, arranged according to the year of birth, shows the steady increase in the cases of retrolental fibroplasia from 1946 onwards.

The children I have seen are those for whom application has been made for admission to the Sunshine Homes. They form about one-fifth of the blind children under 5 years of age in England and Wales. Coming from all over this part of the country they form a fairly good cross-section of the blind children in this age group. These figures show just how serious the situation created by retrolental fibroplasia can be. At the present time it is by far the commonest single cause of blindness in children in this country.

Since Terry's first description of retrolental fibroplasia in 1942 many of the theories as to its causation have not been confirmed. There must be many factors concerned in its production but the only two factors which have a proven relationship are prematurity and the effects of supplemental oxygen. That these two have a very definite relationship cannot be denied. Every report in the last few years appears to implicate them. Table IV shows the relationship with prematurity.

TABLE IV.—BIRTH WEIGHT OF 177 CHILDREN WITH R.L.F. INTERVIEWED AT R.N.I.B. OR IN SUNSHINE HOMES, 1946 TO 1951, WITH DEGREE OF INTELLIGENCE

Birth Weight	No.	Intelligence Normal	Retarded	M.D.	% M.D.
Under 2 lb.	3	3	—	—	—
2 lb. to 2 lb. 15 oz.	97	48	26	23	23·7
3 lb. to 3 lb. 15 oz.	68	37	19	12	17·6
4 lb. to 4 lb. 15 oz.	8	5	2	1	12·5
5 lb. to 5 lb. 8 oz.	1	1	—	—	—
Totals	177	94	47	36	
Percentages	—	53·1%	26·6%	20·3%	

In the 177 cases interviewed they were all under 5½ lb. The greatest incidence appears in the lower birth weights between 2 and 3 lb. The small number occurring in infants under 2 lb. may possibly be accounted for by the smaller chance of survival in infants so immature. There is a very definite decrease in infants over 4 lb.

At these weights and in the group as a whole, 94 of the children (or 53·1%) were of normal

intelligence; 47 (or 26·6%) were retarded but probably educable; while 36 (or 20·3%) were definitely mentally defective. The series is too small to draw any definite conclusions but there does seem to be a significant relationship between birth weight and mental deficiency in an inverse ratio; in those from 2 to 3 lb. 23·7% were mentally defective, from 3 to 4 lb. 17·6%, and from 4 to 5 lb. 12·5%.

It has been suggested that mental deficiency occurs quite frequently in premature infants, but I believe that its incidence in those with retrolental fibroplasia is substantially greater than in premature infants as a whole. This lends some support to those who consider that the process is not simply a local ophthalmic condition in every case but may involve other tissues, especially cerebral tissues, resulting in an encephalo-ophthalmic dysplasia.

The relationship with oxygen also appears definite but the role it plays in the pathogenesis is anything but clear cut. On clinical grounds alone we find that the incidence increased with the advent of incubators and oxygen tents, with perhaps an indiscriminate use of oxygen for most premature infants whether they needed it or not. Where oxygen has been used more carefully and only in conditions where it was necessary to combat asphyxial states the incidence is much less.

Crosse and Evans (1952) have shown that in two of the premature units in Birmingham no cases occurred between 1931 and 1945, a period when little oxygen was used. During 1949 and 1950 when much oxygen was used 5 cases out of 26 survivors between 2 and 3 lb. (i.e. 19·2%) developed retrolental fibroplasia in one unit, while in the other unit 3 cases out of 13 survivors (i.e. 23·1%) developed the condition. During 1951 with only minimal use of oxygen there were no further cases in these units. They also report that the incidence appears to be greater the longer the duration and the higher the concentration of oxygen. It is interesting to note that in this series the survival rate was slightly greater during the same period when less oxygen was given than in former years.

The same situation has been found elsewhere. Although I have not got the figures I understand that in two premature units in Manchester where, a few years ago, oxygen was used freely for most prematures the incidence of the condition was alarming. In these same units for the past two years oxygen has been used only when necessary and in minimal amounts and no new cases have occurred.

The exact role that oxygen has played is less definite. Without going into the detailed work of many investigators the consensus of opinion at the moment is that anoxic conditions, from whatever cause, initiate the pathological process. It was difficult to reconcile this opinion with the clinical observations that the condition developed under circumstances when oxygen was given liberally and over long periods. Ashton and his co-workers (1953), however, in their work on kittens have clarified this. They found that with high concentrations of oxygen the retinal vessels became obliterated, and that some of the collapsed vessels contained trapped coagulated blood. When the oxygen concentration was reduced to that of the atmosphere any remaining patent vessels reopen and form an abnormal network of capillaries, but the normal architecture does not return to integrity. This new blood supply appears inadequate, the new vessels are abnormal and hæmorrhages occur. New blood vessels grow into the vitreous from the disc and retinal detachment develops.

This work seems to confirm the clinical observations of an initial angioblastic response, leading to overgrowth and tortuosity of retinal vessels, with new vasoformative tissue invading the vitreous, with hæmorrhages through the immature capillary walls, leading eventually to gross scarring and detachment of the retina.

Since, however, all premature infants do not respond in this way to high oxygen concentrations, there are undoubtedly other factors concerned. There are still many gaps to be filled in and the problem demands continued thoughtful investigation. But so important is the issue and so intense the interest of those investigating the condition that one feels we can anticipate in the near future the explanation of many of the problems as yet obscure.

There can be few instances in pædiatric and ophthalmic practice where those concerned have got to grips so soon with such a baffling problem. It has been a remarkable achievement of team work and pooling of ideas and although there is a great deal more to be learned about the condition it does seem as though this great tragedy may soon be overcome. Crosse and Evans (1952) sum up the situation when they say—"perhaps it is not too much to hope that in a very few years we shall reach the end of this unhappy interlude in the treatment of the premature infant".

We hope that this optimistic view will be fulfilled. When that times comes we will be in the position that obtained about 1945 when the main causes of blindness in children were due to hereditary and congenital factors. Any reduction in this latter group will call for a concerted and intensive effort on the part of obstetricians, pædiatricians, ophthalmologists and geneticists. At the moment this problem would appear to be beyond us, but it throws out an attractive challenge.

Training and Education of Blind Children

I believe we are apt to take more interest in the physical than in the mental development of children. We should, however, be aware of the importance of the latter. It may not seem to some of us to be so dramatic but it is nevertheless just as important and in many ways even more so. It is with this side that I wish to deal now, although it will be seen that it is impossible to separate the two. Pædiatricians are often asked by the parents of a blind child about the training and care required, especially in the early years. A good physique is important. All the details advised for physical

development of other children apply equally to a blind child, but a little extra care is needed. Because they cannot see there is a tendency in many blind children to be passive. Lack of activity has its effect on appetite, and everything should be done to see that adequate nourishment is taken. For the same reason they tend to be late in reaching the early milestones, and so extra stimulation and encouragement is needed in the matter of sitting up, standing and walking. These are important details, for until a blind child can walk its immediate environment is limited. Once he starts to walk he can explore for himself and his world of interests will be that much larger. Because of his inability to run out or play as actively as other children his muscles are apt to be flabby and lack tone. This increases his tendency to stumble and fall and to make him slow in gaining confidence to get about. Postural defects too are apt to occur. For these reasons it is often advisable to arrange for his attendance at a centre for physiotherapy where he can have massage and exercises to overcome these difficulties.

As well as attention to physical development we must do all we can to develop the child's intellectual potential. This training should begin in early infancy. We must keep in mind that one of the most important avenues of learning, that of sight, is absent, and we must therefore encourage the use of other avenues especially sound and touch. At the same time we must remember that personality and emotional development are important. This is enhanced by ensuring warm affection in order that the child may gain a sense of security. Without this sense of security it may be emotionally disturbed and it will then be less likely to take full advantage of the training of its intellectual powers.

If we realize that blind babies differ amongst themselves in their pattern of character, temperament and intelligence we can see that no rigid set of rules about management can be given. Indeed there is little out of the ordinary about the training. It is essentially the same as for other children except that the blindness must be kept constantly in mind. It is this fact that makes the difference. It makes great demands on the mother and she must learn to give infinitely more time and patience and perhaps courage than would be required for a sighted child.

The mother should try to do most things herself especially as regards the details of nursery routine —feeding, washing, play, and putting to bed. The child should never be left alone while he is awake. He should be in the room where the mother is working, and she should train herself to talk to him while she is carrying out her household duties. In this way he will not feel lonely, and fear of being alone will be prevented. As he gets older she should talk about the things she is doing and arouse his interest in them as much as possible. His interest in surroundings and things must be actively stimulated. While he is in his pram or cot, things to handle should be within easy reach. Not being able to see and to reach out for them himself they must be given to him. He should always have something quite near him so that he can learn early to feel and to investigate small objects which he can hold. Simple objects like a spoon or rattle, or a small tin with something in it to make a noise when he shakes it are better than more complicated toys. A little later he should be allowed to handle all common objects in the home, but everything given to him, even at an early age, should be named each time it is given so that he can associate the words with the objects handled. A special effort should be made in encouraging speech, and no amount of time the mother can afford in talking to him and in trying to make him repeat words intelligently is ever wasted. He must depend a great deal on speech to make his wants known. It is surprising how many blind children one sees even at three years old in whom speech is delayed or limited.

Independence in feeding, washing and dressing comes more slowly than in sighted children, but it should be encouraged as early as possible. Getting him to use a spoon is certainly difficult and much time and patience is required. At first the spoon is filled for him and must be led to his mouth. Later with the use of a rimmed plate he will be able to manage for himself. Clothing should be of a warm but simple nature, with as few buttons as possible. With a little help he will soon be able to manage most things for himself. Once he succeeds he will get a great deal of satisfaction and will take an actual pride in it.

Between 3 and 5 years old a more definite training is required to encourage his sense of touch, and his manipulative ability. Special toys and apparatus can be obtained to help in this. Some of them are quite simple. He should be encouraged in things like threading beads, in building with blocks, in discerning between objects of different size, weight and texture, and later he should have more complicated apparatus which demands a certain amount of reasoning to perform. He must be taught to take an interest in his surroundings, in-doors and out-of-doors, and to mix and play with other children and older people. Some time during the day he should listen to a story and be helped to re-tell it, or encouraged to make one up for himself. In this way all his senses on which he must depend are quickened and developed.

All these suggestions will appear obvious but it is important that the blind child should not be left too much to his own devices. If he is not actively helped in his interests he will tend to make up for them in muscular activity—rocking to and fro, swaying his head from side to side, continuous hopping or jumping, banging his face or chin or poking his fingers in his eyes. These are common mannerisms of the blind and when once established are difficult to correct. They suggest that not enough attention has been given to diverting his interests along more interesting channels.

What about dangers? All the dangers in the home or outside that apply to other children apply even more so to the blind. Fire, hot kettles, tea-pots, water, heavy objects that may be pulled over,

access to windows, road traffic and many more. He must be kept away from all such dangers but he should be taught about them and made to realize what the dangers are. As long as there are no heavy things to pull over on to himself he should be encouraged to walk around the room or flat by himself to explore it. It is a help to have some furniture kept in the same place so that he knows where it is. This helps him to get his bearings. He should be encouraged to walk up and down stairs. It is remarkable how soon they learn to climb and fall about without hurting themselves. Perhaps it is more important to avoid over-protection. So often one meets children who have never been allowed to walk or run, or to go up and down stairs by themselves, and thus lack the confidence in themselves which is so important for them.

What I have tried to convey in this briefest outline is the importance of training in the pre-school years. These are the most formative years in a person's life and the best use must be made of them, so that when school age is reached the child will be in a position to take full advantage at once of the more formal education he will receive there.

In this country a blind child must go to a residential school when 5 years old. Here he learns what sighted children learn and in addition to write and read Braille.

From then on education proceeds very much as for normal children with the result that, depending on their ability, aptitudes and inclinations they are able to pursue many and varied occupations of great interest to themselves and by which they may earn their own living.

Residential Nursery Schools

In this country provision is made for blind children of pre-school age to attend residential nursery schools when this is considered advisable. The question now arises—When is it advisable and at what age should a child go to such a school?

To put it briefly, if a child has a good home and an intelligent and sensible mother with the right temperament, then it should remain at home in most cases till about 3 years of age. But what is a good home and what constitutes a good mother in this respect? I find this very difficult to define. The fact remains that many mothers and homes prove to be adequate and their children progress satisfactorily till they are 3 years old, and in some cases till school age is reached.

But there is a large number of parents who for one reason or another are not able to provide the necessary stimulation, care and training, or suitable environment. Among these one would include : (*a*) Parents whose child is "in care", i.e. where for various reasons they are unable to provide a home for it ; (*b*) Where the mother's health either mental or physical is so unsatisfactory that the child would not receive sufficient wise and loving care if at home; (*c*) Where social and economic circumstances are so difficult that there is danger of the child being neglected, e.g. too large a family of young children; too cramped and dangerous housing conditions; where the child is illegitimate and the mother has to go out to work; and in some cases where the child has to be cared for by aged grandparents; (*d*) Where through ignorance, lack of intelligence, or lack of affection the parents make no attempt to provide affectionate care and adequate stimulation—the child being left in its cot or pram inactive most of the day; (*e*) Where parents are cruel, or neurotic, or hostile; (*f*) Where parents themselves are blind; (*g*) In some cases of blind twins and triplets when the situation so often becomes overwhelming.

For such cases a residential nursery school is, in my opinion, definitely indicated, even in infancy. The problem is, however, not a simple one and the decision regarding admission to such a school must be considered carefully. Whether such schools are desirable or not has prompted correspondence in the Press quite recently. Visitors from this country studying the conditions in the U.S.A. and Canada report that residential schools for various types of handicap are regarded with disfavour in some quarters at least.

Mr. Martin Wilson (1953), the Chief Education Officer for Shropshire, after such a visit poses the question as to whether our system in this country is the right one; and whether it would not be better to have blind children in their own homes and cater for their special needs in their own environment.

Professor W. S. Craig of Leeds (1953) raises an even larger issue when he claims that the care of blind children is part of the greater problem of the care of all handicapped children, and that this in turn is part of the care of child life and health as a whole. He suggests that, wherever practicable, help and care should be brought to the child in his home rather than that the child should have to leave home to secure the necessary aid. He expresses the opinion that residential facilities should be reserved for the selected child with special requirements.

I hope to show that many blind children are in this category and require special facilities which could not be given adequately in their own homes.

Our aim must be to help the child to overcome his handicap as far as possible, to lead him through this important stage of his life when his emotional pattern and intellectual development are beginning to form in such a way that at the end he will be able to take advantage of the particular training he needs to enable him to fit in socially with others, to become independent, and to be able to engage in some occupation or profession so that he may earn his own living or contribute towards it.

I think we would all agree that a state of emotional stability enhances normal intellectual development. A child disturbed emotionally is not in a receptive mood as regards learning. Much has been

said and written in recent years about the value of parental care and especially maternal love and affection in emotional and personality development of children. No one can deny the value of a good home and a good mother in fostering this development. It is one of the important things in a child's early life this sense of security which is fostered by a feeling of love on which he can depend, and without which he may become so disturbed in mind that his chance of normal intellectual development may be impaired, for a time at any rate.

Dr. J. Bowlby (1951) and his team at Tavistock Clinic, in their study of the "Effects on Personality Development of Separation from the Mother in Early Childhood", have produced evidence that in some children at least such separation can have serious adverse effects.

But I think it is right to say that children so affected are in the minority and that other environmental factors before separation occurred may have had a contributory influence in any personality or emotional upset which may have resulted.

In our practice as pædiatricians we can all recall many scores of children who for various disabilities have been away from home for long periods and who, with proper care, have not suffered in any way from emotional disturbances, and have returned home and have led perfectly normal lives.

As regards blind children I believe there are many factors other than separation from parental care which detract from the development of emotional stability, intellectual progress and independence.

Tension in the home on the realization that a child is blind may be intense and an atmosphere is created which is anything but healthy. This is especially so with neurotic parents where over-anxiety may be extreme. Over-anxiety of the parents is often reflected in gross emotional disturbance even in sighted children. Some parents show a lack of care or of helplessness in dealing with such a handicap. They have not got the knack, and the child undoubtedly suffers. Ignorance or lack of intelligence on the part of the parents precludes the possibility of adequate stimulation. Other parents tend to over-protect their children to their great disadvantage. It is quite common to see children 4 or 5 years old almost completely dependent and unable to do even simple things for themselves. A sense of guilt on the part of the parents, or open or unconscious hostility towards the child may lead to rejection. Cramped quarters (and many blind children come from such homes) make it impossible to encourage free movement or the urge to explore. Quite often a child in such circumstances is kept in its pram or cot or a small play-pen for most of the day as nothing else is possible. They tend to vegetate.

Sighted brothers and sisters or children from next door may be a great help in companionship which is necessary, but more often than not their interest in the blind child soon wanes, and they go their own way with their own playmates and ignore and leave the blind one to himself, a circumstance which, sooner or later, must lead to a severe sense of loneliness and frustration.

Some mothers in every way sensible and intelligent find it almost impossible to give the attention and stimulation which is needed. Take the mother of a large family—children to be dressed and fed and sent off to school, housekeeping to be done and shopping attended to, and a busy husband to be catered for at meal-time. Her day is a full one indeed. Add to her responsibilities a blind child who needs all that extra care and thought as regards training which I pointed out at the beginning, and you can see how impossible her task becomes. More often than not the blind child (or the others) must be neglected, not wilfully of course, but simply because she has not the time to do everything.

I submit that these factors have in many cases an equal or even greater adverse effect on the development of emotional stability and independence than has that of temporary parental separation if the child goes to a properly run residential nursery school, and in such circumstances is not likely to develop his intellectual powers as well as he might.

We are fortunate in this country in having nursery schools which are properly run and properly staffed. They are run under the auspices of the Royal National Institute for the Blind and are called "Sunshine Homes". In general it is not the policy of the Institute to accept children under 3 years of age, unless for certain exceptional reasons which I have intimated already. The training given here is very much along the same lines as that suggested at the beginning, but there is the advantage of a quiet and confident attitude of a trained staff without the general anxiety and tension. There is also the advantage of having companionship of children with the same handicap and limitations. A child learns better in an environment where he can compete equally.

Pædiatricians have a special duty in giving advice about what course a parent should take. If home conditions are fully adequate the child may remain at home with advantage until school age is reached. But when all the relevant factors are weighed carefully the pædiatrician will be inclined in many cases, I am sure, to advise admission to a residential nursery school as the best means of providing all the opportunities for physical and mental development to which these children have a right.

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